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National Institute for Health Research

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Abstract

The London Exercise And Pregnant smokers (LEAP) trial: a randomised controlled trial of physical activity for smoking cessation in pregnancy with an economic evaluation

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Background: Smoking during pregnancy is the main preventable cause of poor birth outcomes. Improved methods are needed to help women to stop smoking during pregnancy. Pregnancy provides a compelling rationale for physical activity (PA) interventions as cessation medication is contraindicated or ineffective, and an effective PA intervention could be highly cost-effective.

Objective: To examine the effectiveness and cost-effectiveness of a PA intervention plus standard behavioural support for smoking cessation relative to behavioural support alone for achieving smoking cessation at the end of pregnancy.

Design: Multicentre, two-group, pragmatic randomised controlled trial and economic evaluation with follow-up at the end of pregnancy and 6 months postnatally. Randomisation was stratified by centre and a computer-generated sequence was used to allocate participants using a 1 : 1 ratio.

Setting: 13 hospitals offering antenatal care in the UK.

Participants: Women between 10 and 24 weeks' gestation smoking five or more cigarettes a day before pregnancy and one or more during pregnancy.

Interventions: Participants were randomised to behavioural support for smoking cessation (control) or behavioural support plus a PA intervention consisting of supervised treadmill exercise plus PA consultations. Neither participants nor researchers were blinded to treatment allocation.

Main outcome measures: The primary outcome was self-reported, continuous smoking abstinence between a quit date and end of pregnancy, validated by expired carbon monoxide and/or salivary cotinine. Secondary outcomes were maternal weight, depression, birth outcomes, withdrawal symptoms and urges to smoke. The economic evaluation investigated the costs of the PA intervention compared with the control intervention.

Results: In total, 789 women were randomised ($n = 394$ PA, $n = 395$ control). Four were excluded post randomisation (two had been enrolled twice in sequential pregnancies and two were ineligible and randomised erroneously). The intention-to-treat analysis comprised 785 participants ($n = 392$ PA, $n = 393$ control). There was no significant difference in the rate of abstinence at the end of pregnancy between the PA group (7.7%) and the control group (6.4%) [odds ratio for PA group abstinence 1.21, 95% confidence interval (CI) 0.70 to 2.10]. For the PA group compared with the control group, there was a 33% (95% CI 14% to 56%), 28% (95% CI 7% to 52%) and 36% (95% CI 12% to 65%) significantly greater increase in self-reported minutes of moderate- and vigorous-intensity PA from baseline to 1 week, 4 weeks and 6 weeks respectively. Accelerometer data showed that there was no significant difference in PA levels between the groups. There were no significant differences between the groups for change in maternal weight, depression, withdrawal symptoms or urges to smoke. Adverse events and birth outcomes were similar between the groups except for there being significantly more caesarean births in the control group than in the PA group (28.7% vs. 21.3%; $p < 0.023$). The PA intervention was less costly than the control intervention by £35 per participant. This was mainly attributable to increased health-care usage in the control group. However, there was considerable statistical uncertainty around this estimate.

Conclusions: During pregnancy, offering an intervention combining supervised exercise and PA counselling does not add to the effectiveness of behavioural support for smoking cessation. Only 10% of participants had PA levels accessed by accelerometer and it is, therefore, unclear whether or not the lack of an effect on the primary outcome is the result of insufficient increases in PA. Research is needed to identify the smoking populations most suitable for PA interventions and methods for increasing PA adherence.

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List of abbreviations

AE	adverse event
BCT	behaviour change technique
BMI	body mass index
CI	confidence interval
CO	carbon monoxide
CONSORT	Consolidated Standards of Reporting Trials
DVD	digital versatile disc
EPDS	Edinburgh Postnatal Depression Scale
FTCD	Fagerström Test for Cigarette Dependence
GP	general practitioner
GWG	gestational weight gain
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
ITT	intention to treat
LEAP	London Exercise And Pregnant smokers
MVPA	moderate- and vigorous-intensity physical activity
NCTU	Nottingham Clinical Trials Unit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRT	nicotine replacement therapy
OR	odds ratio
PA	physical activity
PAS	patient administration system
PCT	primary care trust
p.p.m.	parts per million
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SGUL	St George's, University of London
SNAP	Smoking, Nicotine, and Pregnancy

Plain English summary

Smoking during pregnancy damages the growing baby. Most medicines to help with stopping smoking are unlicensed in pregnancy or have been found to be unhelpful. Physical activity (PA) reduces urges to smoke, which are the main cause of smoking relapse. Therefore, we tested whether or not offering a PA programme helps pregnant women to quit smoking.

Women recorded as smokers at their first pregnancy-related visit to the health service were contacted about the study. The 785 women who participated had an equal chance of being offered standard help for stopping smoking given by a health professional or help plus a PA programme that encouraged women to incorporate more activity into their days and provided supervised exercise sessions. We compared women's success at quitting at the end of their pregnancy between the two groups. During their pregnancy women reported how much PA they were doing. Women in the PA group reported doing more PA, although among the 10% of women wearing devices that measured PA objectively there was no detectable difference in PA levels between the two groups. The quit rates were low and were similar for the two groups (7.7% in the PA group, 6.6% in the control group). The PA programme was shown to be reasonably cost-effective, mainly because health-care usage was lower in the PA group. In conclusion, there was no evidence that the PA programme helped women to stop smoking. This may be because the women did not raise their PA levels sufficiently.

Scientific summary

Background

Maternal smoking in pregnancy is the main preventable cause of morbidity and death among women and infants. In most high-income countries at least 10% of women smoke during pregnancy and the prevalence is rising in low- and middle-income nations. There is evidence that behavioural support increases the rate at which women can stop smoking but there is no evidence that smoking cessation medication adds to this. The large majority of women who receive behavioural support for cessation during pregnancy do not manage to stop smoking and thus new options that add to the effectiveness of behavioural support are needed.

Physical activity (PA) programmes may add to the effectiveness of behavioural support. There is convincing evidence that PA reduces the intensity of urges to smoke in the general population of smokers, which are the main cause of relapse to smoking. In non-pregnant smokers, the evidence base showing that PA programmes improve cessation rates is mixed, but most trials did not have sufficiently large sample sizes to have a realistic chance of detecting group differences and had other methodological limitations that increase the risk of bias and make the evidence hard to interpret. Moderate-intensity PA (e.g. brisk walking) is recommended during pregnancy and has been shown to reduce cigarette cravings, and pregnant smokers, especially those who are reluctant to use nicotine replacement therapy, are likely to be receptive to such an intervention. We conducted the London Exercise And Pregnant smokers (LEAP) trial to assess the effectiveness and cost-effectiveness of a PA intervention for smoking cessation during pregnancy.

Objectives

The main objective of the study was to investigate whether or not behavioural support for smoking cessation in pregnancy plus a PA intervention is more effective than behavioural support alone in achieving biochemically validated smoking cessation between a quit date and end of pregnancy. A further objective was to assess the cost-effectiveness of the intervention for achieving smoking cessation at the end of pregnancy.

Methods

The LEAP trial was a pragmatic, randomised controlled trial with an accompanying health economic evaluation. Following their first antenatal booking visit, researchers identified pregnant smokers via lists on the computerised patient administration system at 13 hospital trusts. They discussed the study with potential participants by telephone and enrolled women who consented to participate and met the inclusion criteria. We included women who were between 10 and 24 weeks' gestation, who smoked one or more cigarettes daily at trial entry and who had smoked at least five cigarettes daily before pregnancy. Participants set a quit date and researchers offered six weekly sessions of 20 minutes of individual behavioural cessation support. At enrolment, participants were randomly assigned to behavioural support alone or to behavioural support plus a PA intervention that included 14 sessions of supervised exercise on a treadmill combined with nine PA consultations.

Researchers followed up participants at a visit at the end of pregnancy (valid if between 36 weeks' gestation and 10 weeks after the birth) and by telephone at 6 months postnatally. Researchers retrieved birth outcome data from medical records. The primary outcome was self-reported continuous abstinence from smoking between the quit date and end of pregnancy validated by exhaled carbon monoxide and/or salivary cotinine. Temporary, brief smoking lapses of up to five cigarettes in total were permitted following

the quit day. Secondary outcomes included validated abstinence at 4 weeks after the quit date and self-reported abstinence at 6 months postnatally. Self-reports of PA levels were collected at baseline and weeks 1, 4 and 6 after the quit date, at the end of pregnancy and 6 months post partum. To validate self-reported PA levels, a 10% random subsample of participants had their PA objectively measured using an accelerometer (Model GT1M or GT3X; Actigraph, Pensacola, FL, USA). Ratings of withdrawal symptoms, urges to smoke, confidence for quitting smoking and confidence for participating in PA were recorded. Changes in maternal depression were examined between baseline and end of pregnancy and 6 months after the birth. Changes in maternal weight were assessed between baseline and end of pregnancy. Maternal and fetal adverse events (AEs) and birth outcomes were collected from hospital records.

Based on a systematic review it was anticipated that there would be a cessation rate of 15% in the control group, on the basis that 9% of pregnant women who are smokers stop smoking with usual care after their first antenatal visit and an additional 6–7% quit with behavioural support. Based on pilot work, a cessation rate of 23% was anticipated in the treatment group. The aim was to recruit 866 participants, providing 83% power at a 5% significance level to detect an 8% absolute difference in the rate of smoking cessation at the end of pregnancy between the two groups, corresponding to an odds ratio (OR) of 1.69.

Analysis was on an intention-to-treat (ITT) basis; participants with missing outcome data were assumed to be smoking. The proportion of women reporting continuous smoking abstinence at the end of pregnancy was compared between study groups using logistic regression, with adjustment for recruitment centre. Economic analyses assessed the costs of delivering the intervention for each participant in the intervention group compared with the control group and the costs of caring for each woman and her infant during the period between randomisation and the immediate postnatal period.

Results

In total, 789 women were enrolled in the trial. Four women were excluded post randomisation, two because they were enrolled twice in sequential pregnancies and two because they were ineligible at their baseline visit and had been erroneously randomised. Of the 785 women ($n = 392$ in the PA group) included in the ITT analysis, there were 774 singleton births, 10 twin births and one unknown birth as the woman withdrew consent. The follow-up rate for the primary outcome was 88.8% and this was similar for the two study groups.

Adherence

Participants attended a median of four of 14 treatment sessions in the intervention group and three of six in the control group. Women in the intervention group increased their PA levels more than women in the control group. For the PA group compared with the control group, the percentage increase in minutes of moderate- and vigorous-intensity PA was 33%, [95% confidence interval (CI) 14% to 56%] at 1 week, 28% (95% CI 7% to 52%) at 4 weeks and 36% (95% CI 12% to 65%) at 6 weeks ($p < 0.001$). Relative to baseline there was a decrease in self-reported minutes of PA at the end of pregnancy and 6 months after the birth for both groups. According to the accelerometer data there was no significant difference in PA levels between the groups.

Smoking outcomes

There was no significant difference in smoking abstinence rates between the two groups. The rate of validated continuous abstinence at the end of pregnancy was 7.7% in the PA group and 6.4% in the control group (OR for PA group, adjusted for centre only, 1.21, 95% CI 0.70 to 2.10). At 4 weeks the validated abstinence rate was 12.8% in the PA group and 15.5% in the control group (OR, adjusted for centre only, 0.79, 95% CI 0.53 to 1.18). At 6 months postnatally the self-reported abstinence rate was 6.1% in the PA group and 4.1% in the control group (OR, adjusted for centre only, 1.55, 95% CI 0.81 to 2.97).

Psychological outcomes

Between baseline and 1 week post quit, the PA group exhibited a significant increase in ratings of confidence for participating in PA relative to the control group ($p = 0.002$); however, across this period there was no significant difference in change in ratings for individual cigarette withdrawal symptoms or for urge to smoke or confidence for quitting. There was no evidence of any difference in changes in depression between the two study groups.

Birth outcomes

Birth outcomes were similar between treatment groups. The only significant difference was that more caesarean births occurred in the control group than in the PA group (28.7% vs. 21.3%; $p < 0.023$).

Maternal weight gain

There was no evidence for any difference in maternal weight gain between the two study groups.

Adverse events

The rates of AEs and serious adverse events (SAEs) were similar in the two study groups. The number of women or their infants who had at least one AE or SAE was 55.4% in the PA group and 55.7% in the control group.

Economic analyses

The total mean cost (cost of delivering the intervention plus resource use costs) was £35 per participant lower in the PA group than in the control group. This was mainly attributable to increased health-care usage in the control group. However, as shown by the scatterplot, there was substantial uncertainty around this estimate.

Conclusions

Supplementing behavioural support with a PA intervention was no more effective than behavioural support alone in promoting smoking cessation. These findings were observed despite the PA group self-reporting 35–47% greater increases in PA than the control group during the intervention period. There was no evidence that the PA intervention increased AEs or had a harmful effect on birth outcomes and there was some evidence that the PA intervention resulted in fewer caesarean sections. In pregnancy, the PA intervention that we tested is not recommended for smoking cessation but remains indicated for general health benefits.

Recommendations for research

1. It is not recommended to fund further large-scale trials of PA for smoking cessation until much less expensive observational studies have been conducted to provide promising leads, for example to investigate the populations most suitable for such interventions and methods for increasing PA adherence.
2. The reasons for pregnant smokers' low levels of attendance at supervised PA sessions should be investigated, with the aim of using the findings to increase attendance rates. For example, following on from recent work on barriers to PA, further research is needed to explore barriers to attendance and to PA adherence during pregnancy, and to assess whether or not these barriers vary during different stages of pregnancy and vary among women with different comorbidities, including gestational diabetes and obesity.
3. Further methods of increasing PA adherence among pregnant smokers need to be developed and tested. For example, financial incentives have shown some benefit for aiding smoking cessation in this population and they may be used in combination with PA to increase both attendance at exercise sessions and smoking cessation. In addition, interventions are needed that provide regular prompts to remind women to exercise (e.g. text messages or brief telephone calls); such interventions have been successfully piloted with young women but not yet with pregnant women.

4. The reasons why few inactive pregnant smokers were attracted to a PA trial need to be identified and methods are needed to attract these less active pregnant smokers.
5. Studies are needed to establish whether or not the previously reported finding of a short bout of PA reducing cigarette cravings in pregnant smokers is a robust finding. So far, only one study has investigated this issue. If it is a robust finding, interventions need to be developed that can translate this benefit into prevention of smoking relapse.
6. There was no evidence of beneficial effects on maternal weight gain or depression. Studies are needed that focus on women who are at risk of higher maternal weight gain and women who have high levels of depression at baseline.
7. Among pregnant smokers there was no evidence for a PA intervention having an added benefit for smoking cessation beyond that of usual care. However, it is possible that in some circumstances a PA programme alone may be more practical and may aid smoking cessation and this needs to be assessed.
8. There were significantly fewer deliveries by caesarean section in the PA group than in the control group. Further studies are needed to replicate this finding and to explore the underlying mechanisms.

Implications for health care

There was no evidence that offering regular supervised exercise and PA consultations in addition to routine smoking cessation support to women following their first antenatal visit was effective for aiding smoking cessation. Nor was there any evidence for the PA intervention moderating cravings/urges to smoke but it is possible that there are some acute benefits of PA on reducing cravings during pregnancy and the recommendation to use PA to manage cravings acutely remains for all smokers, including those who are pregnant. The PA intervention did not show any benefit for reducing maternal depression and there was no evidence for an effect on maternal weight gain. There was no evidence of increased AEs in the PA group and there was some evidence for a reduced incidence of caesarean sections; therefore, in line with current guidance, PA remains indicated for general health benefits in pregnancy, including among pregnant smokers.

Trial registration

This trial is registered as ISRCTN48600346.

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Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

The problem of smoking in pregnancy

Maternal smoking in pregnancy is the main preventable cause of morbidity and death among women and infants. Smoking is associated with adverse pregnancy and birth outcomes, including miscarriage, stillbirth, prematurity, low birthweight, congenital abnormalities, and neonatal or sudden infant death.[1–3] Smoking also presents immediate risks for the mother, including placental abruption,[4] as well as the longer-term risks reported for smokers in general. In addition, the children of mothers who smoke are twice as likely to become smokers.[5] Smoking in pregnancy is a global public health problem. In high-income countries the prevalence of smoking in pregnancy is typically between 10% and 25% and it appears to be reducing.[6–10] However, rates seem to be rapidly increasing in low- and middle-income countries.[11] In the UK it is estimated that 12% of women smoke during pregnancy[7] and, as in other high-income countries, rates of smoking in pregnancy remain highest among younger women and those who are more socially disadvantaged.[7] Smoking cessation during pregnancy improves maternal and birth outcomes,[12] yet only approximately 25% of pregnant smokers stop for at least part of their pregnancy and around two-thirds of these relapse after giving birth.[13]

Treatments to aid smoking cessation in pregnancy

Face-to-face and 'self-help' behavioural support are the only two interventions that have been shown to help pregnant women to stop smoking.[12,14] Regular sessions of face-to-face behavioural support can increase smoking cessation rates in pregnancy by approximately 6%[15] and there is a need to identify other interventions that are effective during pregnancy when combined with this support. The most effective therapy in non-pregnant smokers is a combination of behavioural support plus nicotine replacement therapy (NRT), bupropion or varenicline.[16–18] However, the efficacy of NRT during pregnancy is not known,[19] and thus many pregnant women are reluctant to use it,[20] and other smoking cessation medications are contraindicated during pregnancy.[19] There is a need to identify other non-pharmacological interventions that are effective for smoking cessation during pregnancy.

Evidence for physical activity aiding smoking cessation

Effective pharmaceutical aids for quitting are thought to work mainly through reducing cigarette cravings[18] and there is good evidence from a meta-analysis[21] to show that physical activity (PA) reduces these cravings, particularly at a moderate or vigorous intensity. Therefore, PA interventions could aid smoking cessation. For non-pregnant smokers, a Cochrane systematic review[22] has considered the evidence for PA aiding cessation. The majority of the 15 randomised controlled trials (RCTs) reviewed had low statistical power to detect a meaningful difference between the treatment groups, with seven trials having < 25 participants in each treatment arm. Six adequately powered trials compared a group receiving a PA intervention combined with behavioural support with a group receiving behavioural support alone. Three of these studies showed significantly higher smoking abstinence rates in the PA group than in the control group at the end of treatment.[23–25] One of these studies also showed that a PA intervention increased abstinence compared with a control group at the 3-month follow-up and there was a benefit of exercise of borderline significance [relative risk (RR) 2.19, 95% CI 0.97 to 4.96; $p = 0.05$] at the 12-month follow-up.[23] A further study showed significantly higher abstinence rates for the exercise group than for the control group at the 3-month follow-up, but not at the end of treatment or at the 12-month follow-up.[26] The study with the most intensive PA intervention, entailing thrice-weekly sessions of supervised vigorous-intensity exercise, showed the strongest effect on abstinence.[23] The other studies involved PA interventions that were relatively less

intense, particularly in terms of the extent of supervised exercise, and it is possible that supervised exercise is needed for efficacy. Adequately powered trials are needed that involve moderate-intensity exercise, which is likely to be more acceptable than vigorous exercise for most individuals.[27] Moderate-intensity PA (e.g. brisk walking) is recommended for pregnancy[28] and has been shown to reduce cigarette cravings during pregnancy,[29] and pilot work suggests that pregnant smokers are likely to be receptive to a PA intervention.[30]

The effects of physical activity on maternal depression and weight gain

Important secondary outcomes included changes in maternal depression and weight. Antenatal and postnatal depression are important because they are common and are associated with harmful consequences for the mother and child.[31–38] Interventions are needed for preventing and treating these types of depression. Moreover, pregnant smokers are at a heightened risk of depression during and after pregnancy, and women who quit smoking during pregnancy are more likely to relapse if they experience depressive symptoms.[12,39,40] Thus, it is important that pregnant women who smoke or who are attempting to quit are offered effective interventions for depression. The London Exercise And Pregnant smokers (LEAP) trial was the first study to assess the effectiveness of a PA intervention for symptoms of antenatal and postnatal depression specifically among smokers.

Excessive gestational weight gain (GWG) is associated with adverse pregnancy outcomes, including large-for-gestational-age infants and caesarean section.[41,42] In addition, smoking cessation is associated with GWG.[43] Interventions for managing GWG are needed, especially among women attempting to quit smoking, and PA has potential in this regard. Observational studies have demonstrated an association between participation in PA and reduced risk of excessive GWG,[44–46] whereas a recent meta-analysis using data from 10 RCTs showed an overall benefit of participation in PA compared with a control condition in terms of reducing GWG.[47] We are not aware of any studies that have examined the effect of a PA intervention on GWG in pregnant smokers. Among non-pregnant smokers, there is some evidence that PA interventions can limit post-smoking cessation weight gain.[48] The LEAP trial was the first large RCT to examine the effect of a PA intervention on preventing excessive GWG and postnatal weight retention.

Summary

In summary, smoking in pregnancy is extremely harmful for mother and baby and is an enduring global public health problem. Behavioural support is the only smoking cessation intervention shown to be effective in pregnancy. The evidence for PA programmes aiding smoking cessation is mixed and pregnancy provides a compelling rationale for their use because medication is contraindicated or ineffective. We conducted the LEAP RCT to assess the effectiveness of a PA intervention for smoking cessation during pregnancy.

Main objective

The main objective of the study was to investigate whether or not standard behavioural support for smoking cessation in pregnancy plus a PA intervention is more effective than behavioural support alone in achieving biochemically validated smoking cessation between a quit date and the end of pregnancy for women between 10 and 24 weeks' gestation who currently smoke one or more cigarettes daily and who smoked at least five cigarettes daily before pregnancy. A further objective was to assess the cost-effectiveness of the intervention for achieving smoking cessation at the end of pregnancy.

Chapter 2 Methods

Trial design

The LEAP trial was a multicentre, pragmatic, randomised controlled, parallel-group trial of a PA intervention. Participants were monitored from their recruitment at between 10 and 24 weeks' gestation until the end of pregnancy and were then followed up by telephone at 6 months after the birth. The trial protocol has been published.[49]

Participants and recruitment

Eligibility criteria

Eligible participants were aged 16–50 years, were between 10 and 24 weeks' gestation (subject to confirmation that they had a scan to show a viable pregnancy), were currently smoking at least one cigarette per day, were smoking at least five cigarettes per day before pregnancy, were prepared to quit smoking 1 week after enrolment and could confirm that they were able to walk continuously for at least 15 minutes. Women were excluded if they were unable to complete self-administered questionnaires in English (because of a lack of resources for translators) or if they reported any medical condition that might be exacerbated by exercise. There are no documented contraindications to moderate-intensity exercise but if a woman had been advised by her doctor or midwife not to take exercise during pregnancy, if she had any complications during her pregnancy or if she had been cautioned against taking exercise,[28,50] a consultant obstetrician and gynaecologist at her hospital were consulted to check that it was safe for her to participate. Participants joining the trial were monitored at each treatment session for cautions to exercise and adverse events (AEs). Those with drug or alcohol dependence were excluded as the intervention described was not comprehensive enough to address these issues.

Although NRT is licensed for use in pregnancy, there is no evidence for its effectiveness at this time[19] and many pregnant smokers prefer not to use it.[20] Allowing study participants to use NRT might create confounding; therefore, women who indicated that they wished to use NRT on commencing their quit attempt were excluded. Following guidelines,[51] those women who were unable to stop smoking after their quit day and who expressed a wish to receive NRT were prescribed NRT by their general practitioner (GP). The participants' GPs, midwives and obstetricians were informed of their patients' participation in the trial.

Recruiting centres

Participants were recruited from 13 hospital antenatal clinics in England. Initially these were at hospitals in the Greater London area: St George's Healthcare NHS Trust (St George's Hospital), Chelsea and Westminster Hospital NHS Foundation Trust (Chelsea and Westminster Hospital), Guy's and St Thomas' NHS Foundation Trust (St Thomas' Hospital), Croydon Health Services NHS Trust (Croydon University Hospital, previously known as Mayday Hospital), Imperial College Healthcare NHS Trust (Queen Charlotte's and Chelsea Hospital and St Mary's Hospital), Epsom and St Helier University Hospitals NHS Trust (Epsom Hospital) and Kingston Hospital NHS Foundation Trust (Kingston Hospital). Five further sites around England were later added to improve recruitment rates: Surrey and Sussex Healthcare NHS Trust (Crawley Hospital), West Middlesex University Hospital NHS Trust (West Middlesex University Hospital), Mid Cheshire Hospitals NHS Foundation Trust (Leighton Hospital), King's College Hospital NHS Foundation Trust (King's College Hospital) and Medway Foundation Trust (Medway Maritime Hospital).

Researchers

At each centre a dedicated research midwife, research nurse or research psychologist undertook all trial-related procedures, including delivering all of the interventions and administering all of the outcome measures. Researchers were trained by the chief investigator/trial manager (Professor Ussher) in research procedures, including screening, enrolment and consent procedures. They also attended certified Good Clinical Practice training. Researchers were trained to national standards to provide behavioural support for smoking cessation and PA.[52]

Recruitment and consent

The smoking status of all pregnant women is routinely recorded in the hospital computerised patient administration system (PAS) at the first antenatal booking visit, which is typically at 9–14 weeks of gestation. At this time, the hospital midwife informs all women recorded as smokers that it is hospital policy to telephone them to offer smoking cessation support. This support would usually be offered by their local NHS Stop Smoking Service but during the period of recruitment to the study a trial researcher telephoned the women. The following methods of recruitment were used:

- On recording women as smokers, hospital midwives routinely passed referral forms to the researcher. In some cases these referral forms would be available before the smoking status of the women was recorded in the PAS and in these cases the researcher extracted the women's contact details from the referral forms rather than from the PAS.
- In cases in which a woman's smoking status appeared in the PAS before a midwife referral form was received, the researcher extracted the woman's contact details from the PAS and telephoned her. Following our consultation with the Patient Information Advisory Group, the ethics committee gave us permission to contact all pregnant women recorded as smokers. This is because during the trial the researchers were considered as part of the clinical care team and it is routine practice to contact women in this way.
- A flyer containing brief information about the trial was included in women's packs for their first antenatal booking appointment and women were invited to call a researcher if they were interested in finding out more about the study.
- Women who had seen posters advertising the study in hospitals or children's centres could contact a researcher directly.
- We had initially planned to distribute a questionnaire at the first ultrasound visit inviting women to take part. This approach was piloted at several sites in the first month of the study; however, it had a low response rate and was labour intensive and, therefore, was abandoned.

Those who were interested in receiving help with quitting were invited to join the trial or were offered referral to the primary care trust (PCT), as per usual practice. Those women expressing an interest in volunteering were screened for eligibility by the researcher by telephone (see *Appendix 1*) and eligible women were sent a participant information sheet.

After having the chance to consider the participant information sheet for at least 24 hours and to discuss the study with the researcher, women who volunteered were offered an appointment at a community-based children's centre or at their local hospital. At the first appointment they gave their written informed consent before trial data were collected. In addition to trial participation, women were asked to give consent for researchers to have access to their and their child's medical records, for information held by the NHS to be used to keep in touch with them and to follow their health status, and for the researcher to inform their GP, midwife and obstetrician about their participation in the study.

Interventions

The interventions followed Consolidated Standards of Reporting Trials (CONSORT) guidelines for non-pharmacological interventions.[53,54] Delivery of the interventions was standardised by training and by the therapists following manuals (see *Appendices 2* and *3*). The initial competence of the therapists was assessed by the trial manager/chief investigator by observing role-play scenarios during training. The fidelity of the interventions was monitored during the first 6 months by regular observations (at least five intervention sessions) by the trial manager/chief investigator, with the tasks listed in *Appendices 2* and *3* used as a checklist. All sessions were face to face and one to one and were delivered in a private room at the hospital or in a community health centre/children's centre. Social cognitive (learning) theory[55] was the theoretical basis for the interventions. This theory recognises the interplay of individual factors (e.g. self-efficacy to quit smoking or increase PA) and social/environmental factors (e.g. social support) in health behaviour change. For each session that they attended, the women were paid £7 for their travel expenses.

Control group

Those in the control group received behavioural support for smoking cessation, which is generally provided by the NHS Stop Smoking Service to pregnant women as part of 'usual care'. By extracting the elements of the intervention from written manuals and materials provided by the programme (see *Appendix 2*), the contents of the intervention were classified in accordance with the taxonomy of behaviour change techniques (BCTs) described by Michie and colleagues[56] and used in individual behavioural support for smoking cessation (*Table 1*). Participants were offered six weekly sessions of 20 minutes of behavioural support for smoking cessation, commencing 1 week before the quit date and ending 4 weeks afterwards. The intervention (*see Table 1*) incorporated all 43 BCTs for smoking cessation defined by Michie and colleagues,[56] except for the BCT 'provide rewards contingent on successfully stopping smoking', although financial rewards were offered to increase compliance (*Table 2*). Continued support was offered to women who failed to quit or who relapsed to smoking.

Treatment group

In addition to behavioural support for smoking cessation, those in the PA group received a PA intervention, combining PA consultations and supervised exercise. By extracting the elements of the PA consultation from the written manuals and materials of the PA programme (*Table 3*), the contents of the PA consultation have been classified in accordance with the taxonomy of Michie and colleagues[57] of BCTs used to help people change their PA behaviours. There were 14 sessions of supervised exercise, twice a week for 6 weeks (one session with behavioural support for smoking cessation) and then weekly for 2 weeks. Following a familiarisation session at the first visit, participants were advised to aim for 30 minutes of continuous treadmill walking during each session. Following guidelines,[58] moderate-intensity exercise was prescribed according to age and current activity levels and was monitored using a polar heart-rate monitor. The intensity of exercise was also guided by a rating of perceived exertion[59] ('fairly light' to 'somewhat hard') and by the 'talk test', which indicates that the intensity of activity is too high if it is not possible to hold a conversation.

At the first two treadmill sessions and then on every other occasion women were offered a 20-minute PA consultation (total of nine sessions) on increasing their additional 'home-based' PA. The researcher worked through a booklet with each participant (*see Appendix 4*), which the participant retained. The intervention (*see Table 3*) incorporates 19 of 40 BCTs for increasing PA as defined by Michie and colleagues.[57] In general, the consultations aimed to identify opportunities to incorporate PA into women's lives, to motivate them to use PA to aid smoking cessation and to help them use behavioural strategies to improve adherence to these plans. These consultations were tailored towards the women's preferences for PA and their environment, including preference for type of PA, level of support from family or friends and availability of time and facilities for exercise. The participants were encouraged to view PA as a self-control strategy for reducing cigarette cravings and withdrawal[60] and to maintain any increases in PA after their pregnancy. Following recommendations for pregnancy,[28,61] the women were advised to be active for continuous periods of at least 10 minutes at a time, progressing towards accumulating 30 minutes of

TABLE 1 Behaviour change techniques used in the smoking cessation consultations

Week	Session number	Session content	BCTs used (Michie categories[a])
1	Session 1 (1 week before quit day)	Explain the treatment, including the timing of quit	RC4, BS4
		Measure expired CO level and explain purpose	RC3
		Assess and discuss current and past smoking behaviour	RI1
		Identify reasons for wanting and not wanting to quit	BM9
		Assess current motivation/confidence for quitting	RI2
		Discuss past attempts at quitting	RI3
		Prepare for the quit attempt	BM6, BS3
		Discuss use of social support	A2
		Advise on reducing smoking cues	BS8
		Advise subject to note the times when they are likely to relapse	BS6
		Facilitate relapse prevention planning and coping	BS2
		Identify barriers to quitting and address these barriers	BS1
		Emphasise choice (e.g. when they take their final smoke)	RD2
		Provide information about the consequences of smoking during pregnancy	BM1, RC5
		Explain about quitting abruptly, rather than cutting down	BM10
		For all sessions:	
		Allow time for questions	RC2
		Summarise	RC9
		Use reflective listening	RC7
		Elicit participant's views	RC8
		Build a general rapport	RC1
		Give praise for progress	BM7
		Tailor the interactions	RD1
2	Session 2 (quit day)	Look for reasons why the woman is a good prospect	BM2, BM3
		Explain about cigarette withdrawal symptoms and strategies for dealing with them	RC6
		Identify barriers to quitting and address these barriers	BS1
		Advise on avoiding social cues for smoking	BS11
		Advise on changing routine	BS7
		Advise on conserving mental resources	BS10
		Set graded tasks (e.g. take 1 hour/day at a time)	BS9
3	Session 3 (1 week after quit day)	Check smoking status	BS5
		Assess withdrawal symptoms	RI4
		Reassure about the norms for these symptoms	RC10, BM5
		Advise subjects to monitor when they want to smoke	BS6
		Assess CO level and give feedback about whether or not reading has reduced	BM11, BM3
		Discuss planning and coping strategies to prevent relapse	BS2
		If they have relapsed ask them to commit to a new quit date	BM6
		Advise about use of NRT	A1
		Liaise with PCT about obtaining NRT	A3
		Encourage subject to see themselves as a non-smoker	BM8
		Remind them of lottery prize for attending all sessions	BM7

TABLE 1 Behaviour change techniques used in the smoking cessation consultations (*continued*)

Week	Session number	Session content	BCTs used (Michie categories[a])
4	Session 4 (2 weeks after quit day) onwards	Assess CO level	BM11
		Check smoking status	BS5
		If they are struggling offer further support from PCT	A5
		Discuss relapse prevention planning and coping strategies for after birth	BS2, BM8
		Emphasise importance of not having a single puff	BM6
		If subject has relapsed, set a new quit date and review use of NRT	A4

CO, carbon monoxide.

a Michie categories are defined as follows:
Specific focus on the target behaviour (B) and maximising motivation (M). BM1: provide information on the consequences of smoking and smoking cessation; BM2: boost motivation and self-efficacy; BM3: provide feedback on current behaviour; BM5: provide normative information about others' behaviour and experiences; BM6: prompt commitment from the client there and then; BM7: provide rewards contingent on effort or progress; BM8: strengthen ex-smoker identity; BM9: identify reasons for wanting and not wanting to stop smoking; BM10: explain the importance of abrupt cessation; BM11: measure CO level.
Maximising self-regulatory capacity and skill (BS). BS1: facilitate barrier identification and problem-solving; BS2: facilitate relapse prevention and coping; BS3: facilitate action planning/develop treatment plan; BS4: facilitate goal setting; BS5: prompt review of goals; BS6: prompt self-recording; BS7: advise on changing routine; BS8: advise on environmental restructuring; BS9: set graded tasks; BS10: advise on conserving mental resources; BS11: advise on avoiding social cues for smoking.
Promoting adjuvant activities (A). A1: advise on stop-smoking medication; A2: advise on/facilitate use of social support; A3: adopt appropriate local procedures to enable clients to obtain free medication; A4: ask about experiences of stop-smoking medication that the smoker is using; A5: give options for additional and later support.
General aspects of interaction focusing on delivery of the intervention (RD). RD1: tailor interactions appropriately; RD2: emphasise choice.
General aspects of interaction focusing on information gathering (RI). RI1: assess current and past smoking behaviour; RI2: assess current readiness and ability to quit; RI3: assess history of quit attempts; RI4: assess withdrawal symptoms.
General aspects of interaction focusing on general communication (RC). RC1: build general rapport; RC2: elicit and answer questions; RC3: explain the purpose of CO monitoring; RC4: explain expectations regarding treatment programme; RC5: offer/direct towards appropriate written materials; RC6: provide information on withdrawal symptoms; RC7: use reflective listening; RC8: elicit client views; RC9: summarise information/confirm client decisions; RC10: provide reassurance.

TABLE 2 Financial incentives offered to trial participants

Incentive occasion	Maximum financial incentive (£)	
	PA group	Control group
Annual lottery with three prizes of £100 for attending at least 80% of the treatment sessions	100[a]	100[a]
Travel expenses (£7) for each session attended	98[b] (14 sessions)	42[b] (six sessions)
Follow-up at end of pregnancy	10[a]	10[a]
Follow-up at 6 months after birth	10[a]	10[a]
≥ 5 days of accelerometer data recorded	25[a]	NA
Total	243	162

NA, not applicable.

a Shopping vouchers.

b Cash.

TABLE 3 Behaviour change techniques used in the PA consultations

Week	Session number	Session content	BCTs used (Michie categories[a])
1	Session 1 (1 week before quit day)	Review current PA and discuss PA benefits	1, 2
		Explain and demonstrate use of treadmill and pedometer	7, 21, 22, 26
		Check PA confidence levels using scaling questions	16
		All sessions:	
		Agree PA goals	10
		Provide weekly PA and step-count diaries	16
		Allow time for questions, summarise, use reflective listening, elicit participant's views, build a general rapport	NA
		Give praise for effort and for achieving PA goals	12, 13
1	Session 2	Review PA goals and effect of PA on cravings	7, 9, 10
		Complete cost–benefit analysis for increasing PA	2
		Identify PA barriers and problem solve	8
		Explain and demonstrate exercises in booklet	21, 22, 26
		Provide information on places to exercise	20
		Discuss time management and exercise habits	23, 38
		Plan social support	29
		Provide weekly PA diary and step-count diary	16
2	Session 3 (quit day)	Review PA goals, set heart-rate targets on treadmill	10
		Identify PA barriers and problem solve	8
		Provide weekly PA diary and step-count diary	16
		Check PA confidence levels with scaling questions	8
3	Session 4 (1 week after quit day) onwards	Review PA goals, set heart-rate targets on treadmill	10
		Plan for relapse prevention/coping	35
		Review exercises in booklet	21, 22, 26
		Review social support	29
		Use imagery to encourage identity as an 'exerciser'	34
		Provide weekly PA diary and step-count diary	16
		Reminder that sessions reduce to once per week for the last 2 weeks of the programme	27
		Check PA confidence levels with scaling questions	8

NA, not applicable.

a Michie categories are defined as follows: (1) provide information on consequences of behaviour in general; (2) provide information on consequences of behaviour to the individual; (7) action planning; (8) barrier identification/problem-solving; (9) set graded tasks; (10) prompt review of behavioural goals; (12) prompt rewards contingent on effort or progress towards behaviour; (13) provide rewards contingent on successful behaviour; (16) prompt self-monitoring of behaviour; (20) provide information on where and when to perform the behaviour; (21) provide instruction on how to perform the behaviour; (22) model/demonstrate the behaviour; (23) teach subject to use prompts/cues; (26) prompt practice; (27) use of follow-up prompts; (29) plan social support/social change; (34) prompt use of imagery; (35) relapse prevention/coping planning; (38) time management.

activity on at least 5 days of the week. The emphasis was on brisk walking, which is popular among pregnant smokers.[62] As a further option, a home-based antenatal exercise digital versatile disc (DVD) and booklet were provided. In addition, participants were given a pedometer for monitoring their daily steps (Digi-Walker SW-200; Great Performance Ltd, London, UK). Pedometers have been shown to increase activity levels in women[63] and are acceptable during pregnancy[64] and among pregnant smokers.[30] Participants were asked to log their daily steps, with the researcher calculating a 10% increment every 2 weeks, gradually progressing towards 10,000 steps a day.[65]

Randomisation and blinding

An independent statistician generated a randomisation list using Stata version 11.2 (StataCorp LP, College Station, TX, USA), with random permuted blocks of random size stratified by recruitment centre. At enrolment the sequence was concealed from researchers, who had to confirm consent and eligibility on an online database before allocation was revealed. The online database was created by the Nottingham Clinical Trials Unit (NCTU) and held on a secure server in accordance with their standard operating procedures. Allocation was concealed from the participant until all baseline assessments had been completed. The sequence of treatment allocations was concealed until interventions had all been assigned and recruitment, data collection and laboratory analyses were complete. Thus, neither participants nor researchers were blinded to treatment allocation during intervention delivery or during outcome assessment.

Data collection

At baseline, researchers recorded demographic characteristics (including age, marital status, number of children, highest educational qualification, ethnicity, occupation, weeks of gestation and history of premature births) and smoking characteristics [including cigarettes smoked per day (now and before pregnancy), weekly urge to smoke (combining ratings of strength and frequency of urges),[66,67] cigarette withdrawal symptoms,[66,67] Fagerström Test for Cigarette Dependence (FTCD) score[68,69] and partner's smoking status]. Depression was assessed with the 10-item Edinburgh Postnatal Depression Scale (EPDS).[70] PA levels in the previous week (bouts of $\geq$ 10 minutes) were assessed for both groups using the 7-day PA interview (see *Appendix 5*).[71] Confidence levels with regard to taking up regular PA[72] and stopping smoking[73] were also recorded. Clothed weight (without shoes) was measured on a digital scale at the first antenatal booking visit by the midwife. The questionnaire showing assessments at baseline, including assessments repeated at further time points, is provided in *Appendix 6*. The timing of data collection is provided in *Outcome measures*.

Recording of adverse events

During all contacts, participants were asked about AEs. Medical records were examined monthly by research midwives for AEs and after delivery for maternal and infant outcome data. Researchers then summarised the descriptions in the case report forms and in the online study database. Descriptions were used to code the AEs according to standard terms in the *Medical Dictionary for Regulatory Activities* [see www.meddra.org (accessed 25 August 2015)]. Fetal deaths were recorded including miscarriage (non-live birth before 24 weeks' gestation), stillbirth (non-live birth at $\geq$ 24 weeks' gestation) and neonatal death (i.e. from live birth to 28 days).

Outcome measures

Timing of outcome measures

During the intervention period, the main assessment points were at 1 week, 4 weeks and 6 weeks after the quit day. The assessment at 1 week, when the vast majority of the sample was retained, was to assess the early impact of the intervention on cigarette withdrawal symptoms, urges to smoke, confidence for quitting and participating in PA and reports of PA. The 4-week assessment is a standard time for measuring short-term abstinence and is when the NHS Stop Smoking Service assesses abstinence. The 6-week assessment was timed to coincide with the end of the stop smoking programme. There were also follow-ups at the end of pregnancy and 6 months after the birth.

Primary outcome to end of pregnancy

The primary outcome was self-reported continuous abstinence from smoking between the quit date and the end of pregnancy, validated by exhaled carbon monoxide (CO) (Smokerlyzer; Bedfont Scientific Ltd, Maidstone, UK) or salivary cotinine (Salimetrics Europe Ltd, Newmarket, UK). Expired CO levels were assessed weekly up to 4 weeks after the quit day and at the end of pregnancy. Saliva cotinine levels were measured at 4 weeks after the quit day and at the end of pregnancy only among those who self-reported having smoked less than five cigarettes in total (on up to five occasions) since the quit day.

The primary outcome was operationalised as follows. *Continuous abstinence* was defined as having smoked less than five cigarettes in total (on up to five occasions) since the quit day.[74] Following an attempt to stop smoking, it is common for smokers to lapse on several occasions before finally succeeding in maintaining long-term abstinence; therefore, within the definition of continuous smoking abstinence it has become standard to allow five such lapses. With regard to *exhaled CO*, the criterion for confirming abstinence was a reading of < 8 parts per million (p.p.m.).[75] CO was assessed weekly up to 4 weeks after the quit day and at the end of pregnancy. With regard to *salivary cotinine*, the criterion for confirming abstinence was a value of < 10 ng/ml.[76] Cotinine was measured at 4 weeks post quit day and at the end of pregnancy.

The aim was to follow up women within 2 weeks of birth; however, it was acceptable for the primary outcome to be taken at any time between 36 weeks' gestation and 10 weeks after the birth.

The primary outcome was dichotomous, that is, abstinent or non-abstinent. For a participant to be classed as abstinent from smoking at the end of pregnancy (i.e. positive primary outcome), the following criteria had to be satisfied:

- At 4 weeks post quit (it was acceptable for this measure to be taken between 25 days and 6 weeks post quit):
  - 'Have you smoked at all since your quit day?' = 'no not even a puff' or 'yes just a few puffs' or 'yes, between one and five cigarettes' or 'missing' (i.e. any response other than 'yes, more than five cigarettes') *and* CO is < 8 p.p.m. *and/or* cotinine is < 10 ng/ml *or* CO or cotinine is missing.
- At the end of pregnancy:
  - 'Have you smoked at all since your quit day?' = 'no not even a puff' or 'yes just a few puffs' or 'yes, between one and five cigarettes' (i.e. any response other than 'yes, more than five cigarettes') *and* CO is < 8 p.p.m. *and/or* cotinine is < 10 ng/ml.

The concentration of either exhaled CO or salivary cotinine was used to validate abstinence; if both measures were available both were required. Some women will not have data for self-report of smoking or biochemical validation at 4 weeks. If these women are confirmed as abstinent at the end of pregnancy it will be considered as a positive primary outcome.

For a participant to be considered as non-abstinent from smoking at the end of pregnancy (i.e. negative primary outcome), the following criteria had to be satisfied:

- At 4 weeks or the end of pregnancy:
  - 'Have you smoked at all since your quit day?' = 'yes, more than five cigarettes'
  - CO or salivary cotinine values do not confirm abstinence
  - has withdrawn from the study (i.e. refuses follow-up)
  - fails to set a quit date that the follow-up assessment can be referenced against.
- At the end of pregnancy:
  - refuses to allow biochemical validation
  - refuses to self-report number of cigarettes smoked
  - unable to contact to confirm smoking status (i.e. lost to follow-up).

Secondary outcomes

Biochemically validated continuous smoking abstinence was also assessed at 4 weeks after the quit day and 6 months after the birth. In addition, we assessed biochemically validated continuous smoking abstinence using a stricter criterion whereby no cigarettes were allowed after the quit day, at 4 weeks after the quit date, at the end of pregnancy and at 6 months postnatally. Self-reported smoking status at 6 months after the birth was reported by telephone and was not biochemically validated. Many women report that, rather than stopping smoking, they reduce their smoking during pregnancy[77,78] and there is some evidence to suggest that a reduction in smoking of $\geq 50\%$ is associated with an increased infant birthweight.[79] Therefore, levels of smoking reduction were assessed for those women who relapsed.

Other secondary outcome measures were changes in urge to smoke, tobacco withdrawal symptoms and confidence for stopping smoking and maintaining regular PA between baseline and 1 week after the quit day. We also assessed changes in depression between baseline, the end of pregnancy and 6 months after the birth, as well as changes in maternal weight between baseline, 4 weeks after the quit date and the end of pregnancy (the women were weighed again at the end of pregnancy by a researcher using the same method as used by the midwife at the first antenatal booking visit).

Further self-reports of PA levels were collected at weeks 1, 4 and 6 after the quit date and at both follow-ups (i.e. the end of pregnancy and 6 months postnatally). To validate self-reported PA levels, a 10% random subsample of participants had their PA levels objectively measured using an accelerometer (Model GT1M or GT3X; Actigraph, Pensacola, FL, USA). Only 90 women were asked to wear an accelerometer as our pilot work showed that most women would not tolerate waist-worn devices and at the start of the study validated wrist-worn accelerometers were not commercially available; therefore, as the only practicable alternative, we used self-reported PA levels in the primary analysis of PA. During the fourth week after the quit date, the accelerometer was worn over the right hip for 7 consecutive days, recording non-water-based activities during waking hours at 1-minute epochs. The Actigraph has been shown to be practicable and valid during pregnancy.[80–82]

The duration of treadmill exercise and attendance rates were also recorded and use of NRT was monitored throughout the intervention period. At the end of pregnancy, follow-up participants were asked if they had received any face-to-face support to stop smoking during their pregnancy beyond that provided in the study.

Finally, the following birth and maternal outcomes were extracted from participants' hospital records:

1. birthweight
2. gestational age at delivery
3. preterm birth (< 37 weeks' gestation)
4. Apgar score
5. cord blood pH
6. neonatal intensive care unit admission
7. elective termination
8. maternal mortality
9. mode of delivery.

Statistical methods

The statistical analysis plan, which is presented in *Appendix 7*, was finalised before any analyses started. The analysis for the primary outcome was conducted by an independent statistician, with allocation to the two study groups concealed until the analysis was completed. Analyses were performed using Stata version 11.2 and IBM SPSS Statistics version 19 (IBM Corporation, Armonk, NY, USA). Throughout, a *p*-value of < 0.05 was taken to indicate statistical significance and 95% confidence intervals (CIs) were calculated.

Sample size

We anticipated a cessation rate of 15% in the control group on the basis that 9% of pregnant women who are smokers stop smoking with usual care after their first antenatal visit and that with behavioural support another 6–7% quit.[15] Based on pilot work,[30] a cessation rate of 23% was anticipated in the treatment group. We calculated that 866 participants would provide 83% power at a 5% significance level (two-sided) to detect an absolute difference of 8 percentage points in the rate of the primary outcome between the two groups, corresponding to an odds ratio (OR) of 1.69 or a RR of 1.53.

The prime aim of assisting smoking cessation in pregnancy is to improve the outcome of the pregnancy. The latest version of the Cochrane review of psychosocial interventions for supporting women to stop smoking in pregnancy showed evidence that such interventions were effective in helping women stop smoking and improving perinatal outcome.[12] For example, the main subgroup in the review consisting of counselling compared with usual care showed a RR of 1.44 for achieving abstinence in late pregnancy, the same outcome that we used. No individual trial of smoking cessation in pregnancy detected differences in perinatal outcomes by intervention status, but the meta-analysis of all trials in the review showed evidence of this. When pooled together, these interventions produced the following RRs for the intervention compared with the control condition: low birthweight RR 0.82 (95% CI 0.71 to 0.94); preterm birth RR 0.82 (95% CI 0.70 to 0.96); increased mean birthweight 41 g (95% CI 18 g to 63 g). Thus, relative increases in the rate of cessation of a similar size to the one that we were aiming to detect have led to meaningful improvements in perinatal outcomes and would be expected to do so in this trial. A power of 80% is generally considered the minimum power for a trial. Based on available evidence, anticipated recruitment rates and budgeting constraints, we increased the power from the minimum of 80% to 83%. The trial as designed had adequate power for a plausible effect size.

Analysis for the primary outcome at the end of pregnancy

Analysis was on an intention-to-treat (ITT) basis; participants with missing outcome data were assumed to be smoking.[74] The proportion of women reporting continuous smoking abstinence at the end of pregnancy was compared between study groups using logistic regression, with adjustment for recruitment centre using fixed effects. Statistical significance was assessed with the likelihood ratio test, with the estimate of effect given as the OR and 95% CI. A secondary analysis adjusted for centre, nicotine

dependence, age, depression, maternal educational level and partner's smoking status, as potentially important prognostic baseline factors.[83] In addition, as it was observed that the vast majority of participants reported high levels of PA at baseline, we tested for an interaction between baseline PA [< 150 minutes per week of moderate- and vigorous-intensity PA (MVPA) vs. ≥ 150 minutes per week of MVPA] and the treatment effect for the primary outcome. For the primary outcome, to assess the influence of the assumption that missing data equals 'smoking' on the effect size, we used the Hedeker method to test various scenarios of the association between smoking and having missing data.[84] Other outcomes for smoking cessation were analysed in a similar way.

Analysis for secondary outcomes

For ratings of withdrawal symptoms, urge to smoke, confidence for quitting smoking and confidence for participating in PA we conducted a series of linear regressions with scores at 1 week post quit as the dependent variable and the two groups, recruitment centre and baseline scores as independent variables. We compared the use of NRT and behavioural support between the two groups using chi-squared tests.

Physical activity outcomes

Self-reported weekly minutes of MVPA were log-transformed (log base 10) to normality and the difference in self-reported PA between the groups over time was analysed using a mixed-effects model to account for within-person correlations over time. In this model, the difference between treatment groups at each time point was estimated with adjustment for visit time, baseline minutes of MVPA, the interaction of visit time and baseline minutes of MVPA, and recruitment centre. The accelerometer data were analysed using KineSoft software (version 3.3.76; Loughborough, UK). Files with at least 10 hours of valid wear time on ≥ 1 day were retained in the analyses. Standard cut-points were used to determine MVPA.[85] Consistent with the self-report data, only MVPA sustained for at least 10 minutes was included in the assessment of validity using correlational analysis. The validity of the self-reports was also assessed by examining the difference between the self-report data and the accelerometer data using a Bland–Altman plot.[86] The two study groups were compared (Mann–Whitney U-tests) for accelerometer reports of MVPA, both when restricting the analysis to bouts of > 10 minutes (to allow comparison with the self-report data) and when including all MVPA, irrespective of duration.

Fetal and maternal birth outcomes

For binary outcomes, fetal and maternal birth outcomes were compared using logistic regression adjusted for recruitment centre. For continuous outcomes we compared study group means using multiple linear regression, again with adjustment for recruitment centre. For fetal outcomes, the primary analysis was of singleton births. We also conducted a sensitivity analysis including multiple births, with clustering of outcomes accounted for using an approach previously published.[87] This adapts methodology previously created for use with cluster RCTs, assuming that each woman is regarded as the 'cluster' and her number of offspring as the cluster size. A chi-squared test was used to compare the total number of women or their infants who had at least one AE or serious adverse event (SAE).

Depression outcome

One participant was randomised but withdrew consent without reason before providing any data. Thus, the sample for the depression analysis consisted of 784 women. All 784 participants provided EPDS data at baseline, with 383 (48.9%) and 279 (35.6%) participants providing data at the end of pregnancy and 6 months postnatally, respectively. First, we checked whether or not those with EPDS data at the two follow-up points (end of pregnancy, 6 months postnatally) had similar baseline characteristics, quit rate at the end of pregnancy and amount of PA reported as those from the total trial sample. Then, we examined whether or not the baseline characteristics of the PA and control participants were similar in the subsamples with EPDS data at the two follow-up points.

To maximise statistical power, the EPDS data were treated as a continuous variable. We used a mixed-effect linear model, adjusted for visit time, baseline EPDS score, the interaction of visit time and baseline EPDS score, and recruitment centre, and presented the estimated difference in score at the end of pregnancy and at 6 months' follow-up for the PA group compared with the control group. This model allows for correlation between the repeated measurements at the end of pregnancy and at 6 months. In a final linear mixed-effect model, analysis was further adjusted for the following potential predictors of postnatal depression: marital status, age at leaving full-time education (as a proxy for socioeconomic status), body mass index (BMI) and young age (i.e. age ≤ 20 years). At the end of pregnancy, as some of the women provided EPDS data before the birth and some after the birth, we used *t*-tests to explore whether or not EPDS scores were similar at these two times.

Maternal weight outcome

First, we compared the subsample providing maternal weight at the end of pregnancy ($n = 271$) with the main LEAP trial sample ($n = 785$) for baseline characteristics and key end-of-pregnancy outcomes that might be associated with weight gain (i.e. quit rates, PA levels and depression scores). As we are conducting separate analyses for those providing an end of pregnancy weight before the birth (GWG) and those providing an end of pregnancy weight after the birth (postnatal weight retention), we performed the latter comparison separately for the subsamples before and after birth. Second, in the combined sample at the end of pregnancy and in the subsamples providing an end of pregnancy weight before and after delivery we compared baseline characteristics between the two randomisation groups. Subsequent analysis adjusted for any baseline differences between groups that might affect weight.

For all analyses the main outcome was the mean change in maternal weight (i.e. weight in early pregnancy minus weight at the end of pregnancy), computed separately for the subsamples providing an end of pregnancy weight before and after birth. Weight change was first compared between the two randomisation groups using linear regression analyses, with adjustment for baseline weight and recruitment centre. All of the regression analyses were then further adjusted for the following potential prognostic factors for weight change during pregnancy: age and number of previous pregnancies. In a sensitivity analysis we further adjusted the results for baby's weight, which is important because women who quit may have bigger babies than those who do not quit, and continuous rate of smoking abstinence at the end of pregnancy. For the subsamples providing an end of pregnancy weight before and after birth, the sensitivity analyses were limited to 140 and 131 participants, respectively, because of missing data for baby's weight and because three sets of twins were excluded.

For the subsample with GWG (i.e. weight measured before birth) it is important to consider that women will have delivered at different weeks of pregnancy; therefore, besides using the change in the crude measure of weight, we computed the change in mean kilograms per gestational week. This was calculated by dividing the total weight gain by the number of weeks of pregnancy. The regression models used for crude weight change were then repeated using weight change adjusted for gestational weeks as the dependent variable. To assess whether or not weight change is modified by the presence of obesity at baseline we also added an interaction between the effect of PA and whether or not the individual was obese at baseline. Weight at early pregnancy was not added to this model because of its colinearity with the assessment of whether individuals were obese or non-obese.

Next, using Institute of Medicine guidance,[88] we investigated what proportion of women gained excessive gestational weight (coded 'yes' or 'no') relative to their early pregnancy BMI. A woman was considered to have gained excessive gestational weight if she was underweight according to her early pregnancy BMI and her GWG was > 18 kg, her weight was healthy and her GWG was > 16 kg, she was overweight and her GWG was > 11.5 kg or she was obese and her GWG was > 9 kg. We used logistic regression analyses to compute ORs of excessive GWG for each BMI category and for the randomised groups. In the final logistic regression model, the results were adjusted for all prognostic factors that were used in the above main analyses, except weight at early pregnancy.

Ethics and governance

An independent Trial Steering Committee met once or twice per year to monitor the conduct and progress of the trial and to address any safety issues. London Wandsworth Research Ethics Committee granted national research ethical approval (reference number 08/H0803/177), with additional local approvals for each recruitment centre.

Trial management

The trial was co-ordinated from a central trial office located within St George's, University of London (SGUL), with the day-to-day running supervised and organised by the trial manager and administrator. The trial was sponsored by SGUL and conducted in accordance with Good Clinical Practice guidelines.[89] The chief investigator/trial manager and administrator received Good Clinical Practice training. Monthly research staff meetings were held at SGUL. There were no stopping rules or plans for interim analysis.

The NCTU provided a web-based database and randomisation system and data management reports. The system was held on a secure server in the NCTU, had a full electronic audit trail and full back-ups of the database were made every 24 hours. All of the outcome data were entered directly into the online forms by the participants or researchers. The database included validation checks whereby responses not meeting expected criteria would be flagged so that data entry errors were minimised.

The National Institute for Health Research (NIHR) Primary Care Research Network adopted the study. For public and patient involvement in the study see *Appendix 8*.

The protocol[49] has been published and includes a description of approved amendments made to the original protocol after the start of recruitment; details of these amendments are given in the following section.

Protocol amendments

1. For the follow-up at the end of pregnancy, the valid period for assessment was originally defined as from 38 weeks' gestation to 2 weeks after the birth. As there were a number of women who could not be contacted during this time frame, the valid period was extended to 36 weeks' gestation to 4 weeks after the birth (approved by the research ethics committee on 18 May 2010). However, because there were still some women being followed up later than 4 weeks after the birth, the valid period was further revised to 36 weeks' gestation to 10 weeks after the birth (approved 31 January 2012). The aim remained to attempt to follow up as many women as possible within 2 weeks of the birth.
2. To provide the women with an incentive to complete the follow-ups at the end of pregnancy and 6 months postnatally, all women who completed these follow-ups were given a £10 shopping voucher for each of the follow-up sessions attended (approved 18 May 2010).
3. Originally, to be eligible women had to report smoking at least 10 cigarettes a day before their pregnancy. We found that a good number of women reported smoking five to nine cigarettes a day at this time. Therefore, we extended the eligibility criteria to include women smoking at least five cigarettes a day before pregnancy (approved 15 September 2010). These women are still likely to be dependent on smoking as there is evidence that women who say they were smoking five to nine cigarettes before pregnancy are back to smoking 14 cigarettes a day at 18 months postnatally.[90]
4. Initially, women had to be between 12 and 24 weeks' gestation to be eligible for the trial. However, after the trial started most of the hospital trusts began offering earlier antenatal booking appointments (before 12 weeks' gestation) and, because we wished to recruit women as early as possible in pregnancy, we revised this eligibility criterion to 10–24 weeks' gestation (approved 31 January 2012).
5. 'Partner's smoking status' was adjusted for in the final model for all of the outcomes related to smoking abstinence; this amendment was approved after publication of the protocol.

Trial extension

The NIHR agreed a 12-month time extension to the trial. This was necessary as the rate of recruitment had been slower than anticipated and several additional recruitment sites had been established. Through careful budgeting, mostly as a result of the researchers working fewer hours and the chief investigator taking the role of trial manager, the majority of this extension was funded within the original budget. An addition to the budget was awarded to extend the contract of the trial administrator.

Chapter 3 Results

Recruitment of participants

Recruitment took place between April 2009 and November 2012. Follow-up at 6 months after birth continued until January 2014. *Figure 1* shows accrual for the original recruitment target of 866 participants, the revised target of 774 participants [agreed with the NIHR Health Technology Assessment (HTA) programme following approval of the trial extension] and the 789 participants who were actually randomised. Four women were excluded post randomisation. Two women (PA group) were enrolled twice in sequential pregnancies and their second enrolment was removed. The other two women (control group) were excluded because they were found to be ineligible at their baseline visit before any data were collected and had been randomised erroneously. When ineligible participants are mistakenly randomised into a trial it is acceptable, within an ITT approach, to exclude their data without risking bias.[91] *Table 4* shows the recruitment numbers for each centre for the final sample size of 785 participants included in the analysis. As shown in *Table 5*, over two-thirds of participants were recruited through midwife referral and over one-quarter through direct calling, through extracting contact information from the PAS. Fewer than 4% of participants were recruited using the other methods combined.

The CONSORT diagram (*Figure 2*) shows the flow of participants through the study to the primary end point at the end of pregnancy. Around 8100 women were recorded as smokers in the PAS. Of these, approximately one-quarter were uncontactable, just over one-quarter said that they were not interested in participating and just under one-third did not meet the inclusion criteria. A breakdown of the reasons for excluding participants is presented in *Table 6*. The main reason for exclusion was 'reports smoking less than one cigarette a day'. Overall, of the 8096 women recorded as smokers at their first antenatal visit, 9.7% (785) were included in the ITT analysis. Of 785 pregnancies, 774 were singleton pregnancies, 10 were twin pregnancies and one was unknown as the woman withdrew consent.

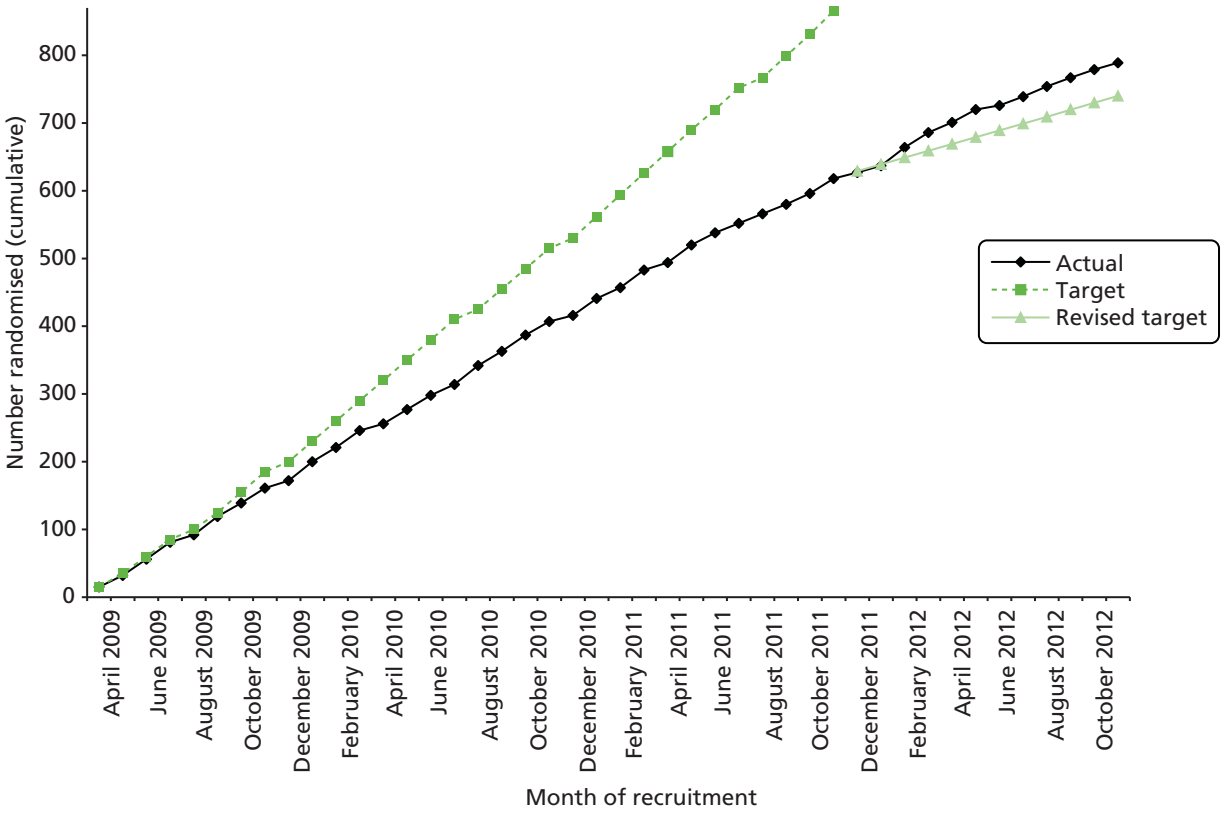

FIGURE 1 Cumulative trial recruitment.

TABLE 4 Recruitment numbers by study centre

Centre	PA group ($n = 392$), n	Control group ($n = 393$), n	Total ($N = 785$), n (%)
St George's Healthcare NHS Trust (St George's Hospital)	44	44	88 (11.2)
Chelsea and Westminster Hospital NHS Foundation Trust (Chelsea and Westminster Hospital)	26	25	51 (6.5)
Imperial College Healthcare NHS Trust (Queen Charlotte's and Chelsea Hospital)	78	76	154 (19.6)
Imperial College Healthcare NHS Trust (St Mary's Hospital)	52	51	103 (13.1)
Guy's and St Thomas' NHS Foundation Trust (St Thomas' Hospital)	21	22	43 (5.5)
Croydon Health Services NHS Trust (Croydon University Hospital)	38	37	75 (9.6)
Kingston Hospital NHS Foundation Trust (Kingston Hospital)	40	41	81 (10.3)
Epsom and St Helier University Hospitals NHS Trust (Epsom Hospital)	47	46	93 (11.8)
Surrey and Sussex Healthcare NHS Trust (Crawley Hospital)	20	20	40 (5.1)
King's College Hospital NHS Foundation Trust (King's College Hospital)	5	5	10 (1.3)
Medway Foundation Trust (Medway Maritime Hospital)	6	7	13 (1.7)
West Middlesex University Hospital NHS Trust (West Middlesex Hospital)	8	10	18 (2.3)
Mid Cheshire Hospitals NHS Foundation Trust (Leighton Hospital)	7	9	16 (2.0)

TABLE 5 Recruitment methods

Recruitment method	%	*n*
Midwife referral	69.3	544
Direct calling after consulting the PAS	27.1	213
Flyer/poster	1.3	10
Ultrasound questionnaire	1.4	11
Referral from PCT or other health professional	0.9	7
Total	100	785

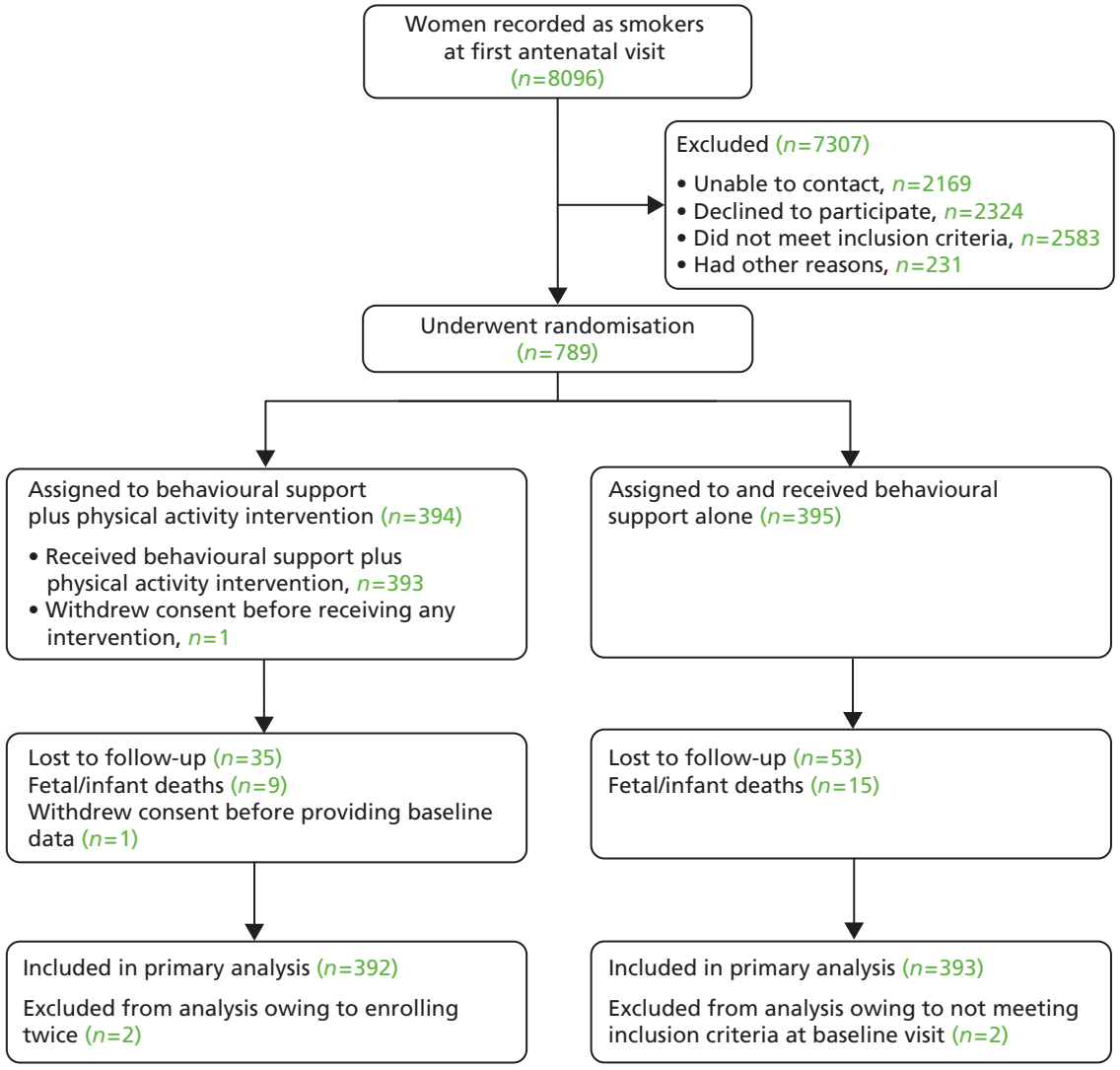

FIGURE 2 Numbers of participants who were enrolled in the study and included in the primary analysis. The participants lost to follow-up included some who had fetal or infant loss and were not assessed for smoking status.

TABLE 6 Reasons for exclusion

Reason for exclusion	%	*n*
Reports smoking less than one cigarette a day now	27.5	710
Gestation > 24 weeks	26.1	673
Gestation < 10 weeks	8.0	207
Unable to attend all visits	13.9	359
Wants to use NRT from commencing quit attempt	11.2	290
Poor English	5.8	149
Drug or alcohol problem	3.1	80
Reports smoking < 10 cigarettes a day before pregnancy	2.1	53
Medical contraindication to exercise	1.2	31
Age < 16 years	0.7	17
Unable to walk for 15 minutes	0.5	13
No permission to contact GP/obstetrician	0.04	1
Total	100	2583

Baseline characteristics

Participants in the two groups had similar baseline characteristics (*Table 7*). Women were recruited to the trial at a mean gestational age of 16 weeks and on average they were 27 years of age. Over half (53.6%) were smoking at least 10 cigarettes a day. By self-report, 70% were achieving the recommendation of 150 minutes a week of MVPA.[27,28]

Follow-up rates

At 4 weeks after the quit day, 316 (80.6%) women were successfully followed up in the PA group and 319 (81.2%) in the control group. At the end of pregnancy follow-up, 587 (74.8%) women were assessed before the birth and 198 (25.2%) were assessed after the birth. The overall follow-up rate for the primary outcome at the end of pregnancy (see *Figure 2*) was 88.8% (697 participants) and there was no evidence of a significant difference in the follow-up rate between study groups. Of the 88 participants (11.2%) who did not complete the assessments necessary for analysis of the primary outcome, 43 (48.9%) were known to have smoked from the follow-up assessments (PA group $n = 19$, control $n = 24$). In addition, of the remaining 45 participants (5.7% of total), 24 had a fetal or infant death and were not asked about smoking status, and one individual withdrew consent; all were assumed to be smoking at the end of pregnancy.

Rates of biochemical validation of smoking status

For the majority of participants who reported that they were not smoking, biochemical validation was obtained. At the end of pregnancy, validation rates for smoking status were 71.4% (30/42) in the PA group and 56.8% (25/44) in the control group ($p = 0.158$); at 4 weeks, the rates were 98.0% (50/51) and 100.0% (61/61) respectively ($p = 0.272$).

TABLE 7 Baseline characteristics according to study group

Characteristic	PA group ($n = 391$[a]), *n* (%)	Control group ($n = 393$), *n* (%)
Age (years), mean (SD)	27.2 (6.1)	27.8 (6.5)
Age at leaving full-time education (years), mean (SD)[b]	17.8 (3.0)	18.0 (3.3)
Maternal weight at first antenatal booking appointment (kg), mean (SD)[c]	68.3 (14.4)	70.4 (15.6)
BMI (kg/m^2), mean (SD)[c]	25.6 (5.0)	26.6 (5.6)
Gestational age (weeks), mean (SD)	15.6 (3.3)	15.6 (3.3)
Number of cigarettes smoked daily before pregnancy, median (IQR)	20 (12–20)	20 (12–20)
Number of cigarettes smoked daily at randomisation, median (IQR)	10 (5–12)	10 (5–15)
FTCD score, median (IQR)[d]	4 (2–5)	4 (2–5)
Expired CO level (p.p.m.), median (IQR)[e]	10 (7–14)	10 (6–14)
Self-report of weekly MVPA (minutes), median (IQR)	210 (125–350)	225 (130–360)
Married or living with partner	230 (58.8)	221 (56.2)
Women with partner who smokes[f]	261 (66.8)	250 (63.6)
Caucasian[g]	308 (78.8)	298 (75.8)
Professional/managerial occupation	46 (11.8)	53 (13.5)
Smoked in a previous pregnancy[h]	186 (78.2)	193 (77.5)
EPDS score of ≥ 13	68 (17.4)	75 (19.1)
Self-report of > 150 minutes per week of MVPA	275 (70.3)	273 (69.5)
Self-report walking as main type of PA	301 (77.0)	313 (79.6)
Parity[i]		
0–1	317 (81.1)	309 (78.6)
2–3	67 (17.1)	75 (19.1)
≥ 4	7 (1.8)	9 (2.3)
Previous preterm birth[j]	68 (17.4)	61 (15.5)
Very or extremely high confidence for quitting smoking	89 (22.8)	98 (24.9)
Very or extremely confident of doing 30 minutes of PA on at least 5 days a week during pregnancy	274 (70.1)	277 (70.5)
Drinks alcohol more than twice a week	6 (1.5)	5 (1.3)
Consumes more than three alcoholic drinks on a drinking day[k]	14 (15.9)	3 (3.8)

IQR, interquartile range; SD, standard deviation.
a Baseline data were not recorded for one participant in the PA group who withdrew consent shortly after randomisation.
b Excludes 41 women who were still in full-time education.
c Weight/BMI not recorded for one participant in the control group.
d Score not recorded for one participant in the PA group.
e CO level not recorded for one participant in the PA group and two in the control group.
f Excludes 92 women who had no partner.
g Race or ethnic group was self-reported and categorised according to standard UK census categories.
h Excludes 297 women who had had no previous pregnancies.
i Parity was defined as the number of previous pregnancies progressing beyond 24 weeks.
j Previous preterm birth was defined as any previous pregnancy that lasted from 24 to 37 weeks.
k Excludes 617 women responding 'not applicable' (i.e. not drinking alcohol).

Attendance at treatment sessions and compliance with the physical activity intervention

Participants attended a median of four of 14 treatment sessions in the PA group and three of six in the control group (*Table 8*). For the PA group compared with the control group, there was a 33% (95% CI 14% to 56%), 28% (95% CI 7% to 52%) and 36% (95% CI 12% to 65%) significantly greater increase in self-reported minutes of MVPA from baseline to 1 week, 4 weeks and 6 weeks respectively (see *Table 8* and *Figure 3*). There was a decrease in self-reported minutes of PA at the end of pregnancy and at 6 months relative to baseline for both groups.

Of 90 participants asked to wear an accelerometer, 78 (86.7%) provided valid data ($n = 37$ PA group), 10 provided insufficient data and two were technical failures. Participants providing accelerometer data had similar baseline characteristics to those in the total sample. The majority (72%) had valid accelerometer data for at least 4 days. During the week of accelerometer wear, the median number of minutes of MVPA per day by self-report and according to accelerometer data was 38.2 [interquartile range (IQR) 25.4–54.5] and 7.8 (IQR 0–16.5) respectively. In total, 87% of participants self-reported higher levels of MVPA compared with the accelerometer data. Self-reports of minutes of MVPA per day were not significantly correlated with the accelerometer data (Spearman's rho = 0.133, $p = 0.247$). Consistent with the correlation, using a Bland–Altman plot the mean difference between the self-report data and the accelerometer data for MVPA was 26.85 (95% CI 20.81 to 32.88) minutes (*Figure 4*). The median number of minutes of MVPA according to accelerometer data, when including only bouts of at least 10 minutes, was very similar for the PA group [7.5 (IQR 0–15.5)] and the control group [8.0 (IQR 0–16.2)] ($p = 0.816$). When including all MVPA, irrespective of duration, median activity levels per day tended to be higher for the PA group [38.00 (IQR 20.00–52.60)] than the control group [31.17 (IQR 19.00–44.10)], although this difference did not reach significance ($p = 0.538$).

Only 28 women reported receiving face-to-face behavioural support for smoking cessation besides that offered in the trial and 60 women reported using NRT; the numbers reporting this support were similar in the two groups.

TABLE 8 Compliance with interventions

Variable	PA group	Control group	Relative change in PA (95% CI): mixed-effect model for the log of PA	*p*-value
Self-reported weekly minutes of MVPA, *n*, median (IQR)				
Baseline	391, 210 (125–350)	393, 225 (130–360)		
1 week post quit	162, 280 (190–425)	206, 240 (140–420)	1.33 (1.14 to 1.56)	< 0.001
4 weeks post quit	135, 270 (180–420)	157, 210 (120–340)	1.28 (1.07 to 1.52)	0.006
6 weeks post quit	90, 277 (180–400)	121, 220 (130–350)	1.36 (1.12 to 1.65)	0.002
End of pregnancy	188, 155 (100–240)	187, 140 (60–240)	1.25 (0.96 to 1.61)	0.093
6-month follow-up	147, 180 (80–330)	136, 135 (60–285)	1.16 (0.85 to 1.59)	0.339
Number of treatment sessions attended, *n*, median (IQR)	391, 4 (2–8)[a]	393, 3 (2–6)	NA	
Time walked on treadmill during supervised exercise (minutes), *n*, mean (SD)				
Baseline	390, 12.2 (7.5)	NA	NA	
1 week post quit	163, 19.0 (8.5)			
4 weeks post quit	134, 15.2 (10.8)			
6 weeks post quit	90, 17.7 (10.9)			

IQR, interquartile range; NA, not applicable; SD, standard deviation.
a The median (IQR) number of sessions attended for PA counselling = 2 (1–4) and for smoking cessation behavioural support = 2 (1–4). Women participated in supervised exercise at all sessions.

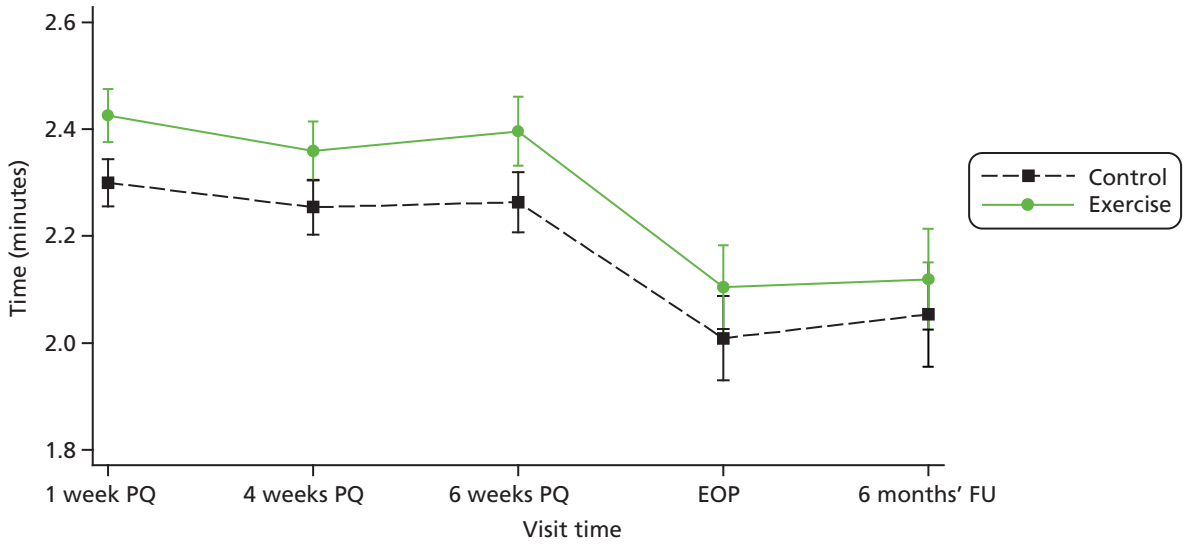

FIGURE 3 Comparison[a] of predicted self-reported levels of MVPA on a log-scale in the trial groups at different time points (bars represent CIs). EOP, end of pregnancy, FU, follow-up; PQ, post quit. a, Prediction on log scale from the mixed-effect model.

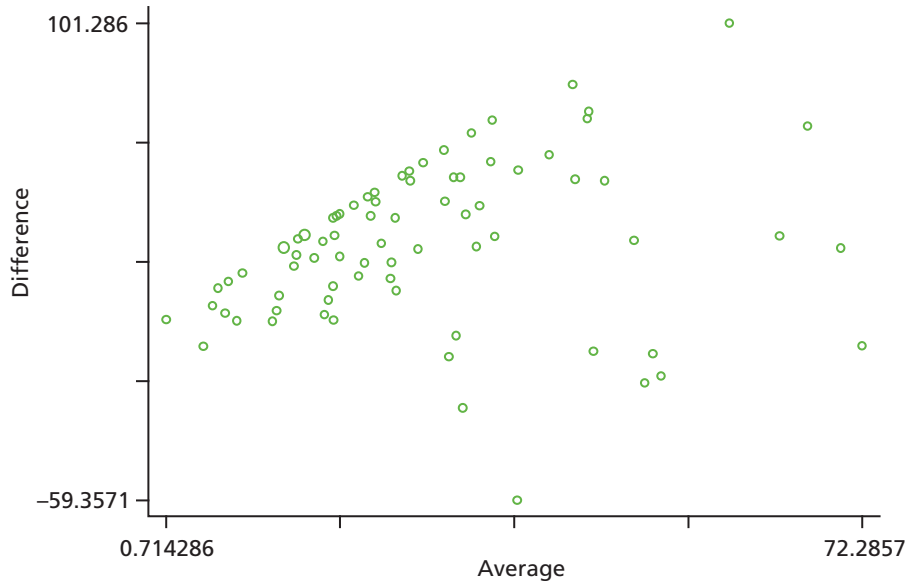

FIGURE 4 Bland–Altman plot of the difference between self-reported MVPA and accelerometer data for MVPA against the average of these measures ($n = 78$) showing the distribution of differences and how they relate to the average. Limits of agreement (reference range for difference) –26.698 to 80.390; range 0.714–72.286.

Smoking abstinence and reduction rates

There was no significant difference in smoking abstinence rates or smoking reduction rates between the two groups at follow-up (*Table 9*). The rate of validated continuous abstinence at the end of pregnancy (primary outcome) was 7.7% in the PA group and 6.4% in the control group (OR for PA group, adjusted for centre only, 1.21, 95% CI 0.70 to 2.10). At 4 weeks the validated abstinence rate was 12.8% in the PA group and 15.5% in the control group (OR, adjusted for centre only, 0.79, 95% CI 0.53 to 1.18). At 6 months postnatally the self-reported abstinence rate was 6.1% in the PA group and 4.1% in the control group (OR, adjusted for centre only, 1.55, 95% CI 0.81 to 2.97). Fully adjusted analyses yielded similar findings (at end of pregnancy: OR 1.37, 95% CI 0.78 to 2.41). The sensitivity analyses showed that the observed effect size and

TABLE 9 Primary and secondary smoking abstinence and reduction outcomes

Abstinence/reduction outcomes[a]	PA group ($n = 392$), *n* (%)	Control group ($n = 393$), *n* (%)	OR (95% CI)[b]	Adjusted OR (95% CI)[c]
Primary				
Self-reported continuous abstinence at end of pregnancy with biochemical validation[d]	30 (7.7)	25 (6.4)	1.21 (0.70 to 2.10)	1.37 (0.78 to 2.41)
Secondary				
Self-reported continuous abstinence at 4 weeks after quit day with biochemical validation[e]	50 (12.8)	61 (15.5)	0.79 (0.53 to 1.18)	0.87 (0.57 to 1.31)
Self-reported continuous abstinence at 6 months after birth	24 (6.1)	16 (4.1)	1.55 (0.81 to 2.97)	1.66 (0.82 to 3.37)
Self-reported lapse-free abstinence with biochemical validation				
At 4 weeks after quit day	17 (4.3)	16 (4.1)	0.68 (0.38 to 1.22)	0.74 (0.41 to 1.34)
At end of pregnancy	20 (5.1)	29 (7.4)	1.07 (0.53 to 2.14)	1.22 (0.60 to 2.48)
At 6 months after birth	10 (2.6)	10 (2.5)	1.04 (0.43 to 2.56)	1.12 (0.45 to 2.78)
	PA group, *n*, mean (SD)	**Control group, *n*, mean (SD)**	**Mean difference (95% CI)**	**Mean difference (95% CI)**
Self-reported reduction in no. of cigarettes smoked daily[f]				
Between baseline and 4 weeks after quit day	67, 4.3 (4.4)	70, 4.0 (4.7)	0.23 (–1.22 to 1.73)	0.27 (–1.16 to 1.65)
Between baseline and end of pregnancy	130, 4.0 (4.7)	119, 2.9 (5.9)	1.13 (–0.26 to 2.55)	1.08 (–0.11 to 2.32)
Between baseline and 6 months after birth	97, 1.4 (4.5)	100, 1.0 (5.3)	0.37 (–0.99 to 1.74)	0.21 (–1.14 to 1.58)

SD, standard deviation.

a Continuous abstinence was defined as having smoked fewer than five cigarettes since the quit day. End of pregnancy was defined as between 36 weeks' gestation and 10 weeks after the birth. Biochemical validation was by exhaled CO level and/or salivary cotinine level; if both measures were available both were required for validation.

b ORs were adjusted for recruitment centre only (as a stratification factor).

c ORs were adjusted for centre, FTCD score at baseline, participant age at randomisation, EPDS score at baseline, age on leaving full-time education and partner's smoking status at baseline.

d The biochemical tests did not validate the report of not smoking (i.e. probable false reporting of cessation) in 12 of 42 women (28.6%) in the PA group and 19 of 44 women (43.2%) in the control group.

e The biochemical tests did not validate the report of not smoking in four of 51 women (7.8%) in the PA group and seven of 61 women (11.5%) in the control group.

f Using linear regression analysis with bootstrap method.

its statistical significance were independent of the influence of missing data for the primary outcome. There was no significant interaction between baseline self-reports of MVPA (< 150 vs. ≥ 150 minutes per week) and the treatment effect for the primary outcome [logistic regression model adjusted for site only: likelihood ratio test (LR chi-squared) = 2.31, $p = 0.129$; similar results were found for the fully adjusted model].

Withdrawal symptoms and urge to smoke

Tables 10 and *11* show the withdrawal symptom and urge to smoke scores, respectively, at baseline and 1 week post quit. When controlling for baseline score and treatment centre there was no significant group difference in total withdrawal score or urge to smoke score at 1 week post quit. When withdrawal symptoms were examined individually there were still no significant group differences.

TABLE 10 Comparison of withdrawal symptom scores between randomisation groups at baseline and 1 week post quit

Follow-up	PA group, *n*, mean (SD) score	Control group, *n*, mean (SD) score	Linear regression: β (95% CI) for PA group vs. control group; *p*-value[a]
Baseline			
Withdrawal symptoms scale total score (range 1–35)	391, 16.3 (4.9)	393, 16.4 (4.7)	
Symptoms			
Restless	2.3 (1.2)	2.3 (1.2)	
Irritable	2.6 (1.2)	2.7 (1.2)	
Depressed	1.8 (1.1)	1.7 (1.0)	
Hungry	2.8 (1.3)	3.0 (1.2)	
Poor concentration	2.0 (1.1)	2.0 (1.1)	
Poor sleep at night	2.5 (1.3)	2.5 (1.3)	
Anxious	2.2 (1.2)	2.2 (1.2)	
1 week post quit			
Withdrawal symptoms scale total score (range 1–35)	163, 16.0 (4.6)	206, 16.6 (4.6)	–0.56 (–1.45 to 0.33); 0.256
Symptoms			
Restless	2.4 (1.1)	2.4 (1.1)	
Irritable	2.7 (1.1)	2.9 (1.2)	
Depressed	1.7 (1.0)	1.8 (1.0)	
Hungry	2.7 (1.2)	2.9 (1.2)	
Poor concentration	2.1 (1.0)	2.1 (1.1)	
Poor sleep at night	2.3 (1.2)	2.3 (1.2)	
Anxious	2.1 (1.0)	2.2 (1.1)	

SD, standard deviation.

a Coefficient (95% CI) for PA group obtained from the linear regression with withdrawal total score at 1 week post quit as the dependent variable and the two groups, recruitment centre and withdrawal total score measured at baseline as independent variables; thus, it is the adjusted difference in withdrawal total score at 1 week post quit for the PA group group vs. the control group.

TABLE 11 Comparison of urge to smoke scores[a] (range 0–10) between randomisation groups at baseline and 1 week post quit

Follow-up	PA group, *n*, mean (SD) score	Control group, *n*, mean (SD) score	Linear regression: β (95% CI) for PA group vs. control group; *p*-value[b]
Baseline	391, 6.2 (2.0)	393, 6.2 (1.9)	
1 week post quit	163, 5.3 (2.0)	206, 5.5 (2.0)	–0.23 (–0.62 to 0.16); 0.242

SD, standard deviation.
a Combination of item for strength of urges and item for frequency of urges.
b Coefficient (95% CI) for PA group obtained from the linear regression with urge to smoke score at 1 week post quit as the dependent variable and the two groups, recruitment centre and urge to smoke score at baseline as independent variables; thus, it is the adjusted difference in urge to smoke score at 1 week post quit for the PA group vs. the control group.

Confidence for participating in physical activity and stopping smoking

Tables 12 and *13* present the scores for confidence for participating in PA and for stopping smoking, respectively, at baseline and 1 week post quit. When controlling for baseline score and treatment centre, ratings for confidence for participating in PA were significantly higher at 1 week post quit in the PA group than in the control group. When making the same adjustments, there was no significant group difference in confidence for quitting smoking at 1 week post quit.

TABLE 12 Comparison of self-confidence for participating in PA between randomisation groups at baseline and 1 week post quit

Follow-up	PA group, *n*, mean (SD) score	Control, *n*, mean (SD) score	Linear regression: β (95% CI) for PA group vs. control group; *p*-value[a]
Baseline	391, 3.9 (1.1)	393, 3.9 (1.0)	
1 week post quit	163, 3.9 (1.0)	157, 3.7 (1.0)	0.30 (0.10 to 0.49); 0.002

SD, standard deviation.
a Coefficient (95% CI) for PA group obtained from the linear regression with self-confidence score at 1 week post quit as the dependent variable and the two groups, recruitment centre and self-confidence score at baseline as independent variables; thus, it is the adjusted difference in self-confidence score at 1 week post quit for the PA group vs. the control group.

TABLE 13 Comparison of self-confidence for stopping smoking between randomisation groups at baseline and 1 week post quit

Follow-up	PA group, *n*, mean (SD) score	Control group, *n*, mean (SD) score	Linear regression: β (95% CI) for PA group vs. control group; *p*-value[a]
Baseline	391, 3.9 (0.9)	393, 4.0 (1.0)	
1 week post quit	163, 4.4 (1.0)	206, 4.3 (0.9)	0.15 (–0.03 to 0.33); 0.097

SD, standard deviation.
a Coefficient (95% CI) for PA group obtained from the linear regression with self-confidence score at 1 week post quit as the dependent variable and the two groups, recruitment centre and self-confidence score at baseline as independent variables; thus, it is the adjusted difference in self-confidence score at 1 week post quit for the PA group vs. the control group.

Birth outcomes

Table 14 shows outcomes for singleton births. These outcomes were very similar between the two study groups except that there were significantly fewer deliveries by caesarean section in the PA group than in the control group (21.3% vs. 28.7%). Analyses that included twin births gave very similar findings.

TABLE 14 Birth outcomes by treatment group[a]

Fetal outcomes (singleton births only)	PA group ($n = 384$), n/N (%)	Control group ($n = 391$), n/N (%)	OR (95% CI)[b]
Miscarriage[c]	6/383 (1.6)	10/389 (2.6)	0.60 (0.22 to 1.67)
Stillbirth[c]	2/377 (0.5)	2/379 (0.5)	1.01 (0.14 to 7.24)
Neonatal death[c]	0	1/391 (0.3)	Not calculated
Preterm birth (< 37 weeks' gestation)	35/356 (9.8)	26/348 (7.5)	1.36 (0.80 to 2.31)
Low birthweight (< 2.5 kg)	38/353 (10.8)	44/359 (12.3)	0.87 (0.55 to 1.38)
NICU admission	27/352 (7.7)	36/356 (10.1)	0.74 (0.44 to 1.25)
Apgar score at 5 minutes < 7	8/344 (2.3)	11/351 (3.1)	0.74 (0.29 to 1.85)
Cord blood arterial pH < 7	2/130 (1.5)	0/125	Not calculated
Congenital abnormalities[d]	9/346 (2.6)	6/348 (1.7)	1.43 (0.50 to 4.12)
Assisted vaginal delivery	46/357 (12.9)	32/359 (8.9)	1.51 (0.94 to 2.43)
Caesarean delivery	76/357 (21.3)	103/359 (28.7)	0.67 (0.48 to 0.95)[e]
	PA group ($n = 384$), mean (SD)	Control group ($n = 391$), mean (SD)	Mean difference (95% CI)[b]
Birthweight (kg)	($n = 354$) 3.13 (0.58)	($n = 359$) 3.15 (0.64)	–0.01 (–0.11 to 0.08)
Gestational age at delivery (weeks)	($n = 356$) 39.24 (2.1)	($n = 348$) 39.26 (2.1)	–0.02 (–0.36 to 0.31)

NICU, neonatal intensive care unit; SD, standard deviation.

a For all outcomes, 10 women with twins ($n = 8$ PA group) were removed from the denominator.

b ORs and mean differences were adjusted for recruitment centre (as a stratification factor).

c These outcomes were defined a priori as SAEs. There were no maternal deaths and no SAEs were judged to be related to the PA intervention. The denominator for miscarriage was calculated as the number randomised minus the number of elective terminations ($n = 3$) (elective terminations are excluded as they do not have the potential to miscarry). The denominator for stillbirth was calculated as the number randomised minus the number of miscarriages and elective terminations (elective terminations and miscarriages were excluded as they do not have the potential to result in a stillbirth). For all other outcomes, the denominator is the number of singleton live births, excluding those births for which outcome data were missing.

d For a list of congenital abnormalities see *Appendix 9*.

e $p < 0.023$.

Adverse events

There were similar numbers of AEs and SAEs in the two groups (*Table 15*). The total number of women or their infants who had at least one AE or SAE was 217 (55.4%) in the PA group and 219 (55.7%) in the control group (OR 0.99, 95% CI 0.75 to 1.32). The full breakdown of the data for less frequent AEs is provided in *Appendix 9*.

TABLE 15 Adverse events according to study group[a]

Event	PA group ($n = 392$), *n* (%)	Control group ($n = 393$), *n* (%)
SAEs		
Maternal death	0	0
Other events[b]	12 (3.1)	13 (3.3)
Maternal AEs potentially related to treatment[c]	2 (0.5)	0
Maternal AEs as probable complications of pregnancy		
Vaginal bleeding or haemorrhage	37 (9.4)	35 (8.9)
Abdominal pain	79 (20.2)	83 (21.1)
Infection in pregnancy	61 (15.6)	55 (14.0)
Premature rupture of membranes at < 37 weeks' gestation	19 (4.8)	16 (4.1)
Gestational diabetes	7 (1.8)	8 (2.0)
Gestational hypertension	13 (3.3)	13 (3.3)
Pre-eclampsia	4 (1.0)	11 (2.8)
Other, less frequent events[d]	105 (26.8)	114 (29.0)
Fetal AEs as probable complications of pregnancy		
Decreased fetal movement	41 (10.5)	49 (12.5)
Intrauterine growth restriction	15 (3.8)	18 (4.6)
Other, less frequent events[d]	7 (1.8)	6 (1.5)
Neonatal AEs	15 (3.8)	14 (3.6)
Total AEs	417	435

a For each study group percentages were calculated as the number of women who had at least one event in any category of AE divided by the number of women who underwent randomisation. Participants may have had AEs in more than one category.
b Other SAEs included miscarriage, stillbirth and neonatal death plus events resulting in a significant disability or incapacity and/or life-threatening events.
c Spotting, nausea.
d Events occurring in < 3% of women or infants; for a list of these *see Appendix 9*.

Maternal depression

All 784 participants provided EPDS data at baseline, with 383 (48.9%) and 279 (35.6%) participants providing these data at the end of pregnancy and at 6 months postnatally, respectively. The baseline characteristics of the subsamples used for the EPDS analysis at the two follow-up points were similar to those for the total trial sample. The baseline characteristics of the two trial groups were also similar in the subsamples at the end of pregnancy and at 6 months postnatally.

In both models the EPDS score was significantly higher in the PA group than in the control group at the end of pregnancy (*Table 16*). At this time there was a mean increase in EPDS score of 0.4 in the PA group and a mean reduction in EPDS score of 0.5 in the control group (mean difference between groups in fully adjusted model 0.95, 95% CI 0.08 to 1.83). When examining the data separately for end of pregnancy outcomes before and after the birth the findings were very similar. There was no significant difference in EPDS score between the groups at 6 months' follow-up (fully adjusted mean difference 0.37, 95% CI –0.59 to 1.33).

TABLE 16 Comparison[a] of maternal depression scores between the randomisation groups at the end of pregnancy and 6 months after birth

Follow-up	EPDS score, *n*, mean (SD)		β (difference between PA and control group, adjusted for baseline EPDS and centre only[b]) (95% CI); *p*-value	β (difference between PA and control group, fully adjusted[c]) (95% CI); *p*-value
	Control group	PA group		
Baseline	393, 7.7 (5.0)	391, 7.6 (5.3)	0	0
End of pregnancy	194, 7.2 (5.0)	189, 8.0 (4.9)	1.06 (0.19 to 1.94); 0.017	0.95 (0.08 to 1.83); 0.033
6 months	133, 6.6 (4.7)	146, 6.8 (4.8)	0.52 (–0.45 to 1.50); 0.293	0.37 (–0.59 to 1.33); 0.450

SD, standard deviation.
a Results from mixed-effect linear model.
b EPDS score as the dependent variable and randomisation groups, follow-up times, baseline EPDS score, interaction between follow-up time and baseline EPDS score, and recruitment centre as independent variables.
c Further adjustment for age at leaving full-time education, young age (≤ 20 years), BMI and marital status in the model in footnote b.

Maternal weight

The combined sample for the analysis of maternal weight at the end of pregnancy was 271 participants, with 140 (51.7%) providing maternal weight before the birth and 131 (48.3%) providing maternal weight after the birth. The characteristics of these two subsamples (i.e. maternal weight provided before and after birth) were comparable with those of the main trial sample except that the rate of continuous smoking abstinence at the end of pregnancy was higher in both the subsample with maternal weight provided before delivery [$n = 35$ (25.0%)] and the subsample with maternal weight provided after delivery [$n = 14$ (10.7%)] than in the main sample [$n = 55$ (7.0%)]. In the combined sample at the end of pregnancy the characteristics were very similar between the two randomisation groups except that there was an approximately 1-kg difference in weight at early pregnancy between the two groups and therefore the results were adjusted for weight at early pregnancy. Rates of smoking abstinence were higher in the PA group than in the control group at the end of pregnancy [$n = 29$ (21.2%) vs. $n = 20$ (14.9%)] but this difference was not significant. When comparing the characteristics between the randomisation groups separately for the subsamples providing maternal weight before and after birth the findings were very similar.

At the end of pregnancy the mean GWG (subsample providing maternal weight before birth) in the PA group was 12.4 kg [standard deviation (SD) 6.1 kg] and in the control group was 11.2 kg (SD 7.0 kg) and the postnatal weight retention (subsample providing maternal weight after birth) was 4.7 kg (SD 7.2 kg) and 4.9 kg (SD 7.3 kg), respectively. With the basic adjustment the mean difference in GWG and postnatal weight retention for the PA group compared with the control group was 1.08 kg (95% CI –1.08 kg to 3.23 kg) and 0.11 kg (95% CI –2.27 kg to 2.49 kg), respectively (*Table 17*). In the fully adjusted model these mean differences were reduced and neither of them achieved statistical significance. The estimated mean weight change per gestation week was 0.31 kg (SD 0.15 kg) in the PA group and 0.27 kg (SD 0.17 kg) in the control group, and the difference was not significant. In contrast, the difference in estimated mean weight change per gestation week between the groups was significantly lower for those classed as obese at baseline than for those classed as non-obese at baseline (–0.12 kg, 95% CI –0.21 kg to –0.03 kg; $p = 0.010$). There was no significant interaction between the effect of PA compared with the control and whether or not the individual was obese at baseline ($p = 0.599$), such that, in those who were not obese, the difference between the PA group and the control group was 0.03 kg (95% CI –0.03 kg to 0.08 kg) and in those who were obese the difference between the PA group and the control group was 0.06 kg (95% CI –0.09 kg to 0.21 kg).

According to Institute of Medicine guidelines[88] the overall proportion of women with excessive GWG was 38.6%. The risk of excessive GWG was slightly higher in the PA group than in the control group (fully adjusted OR 1.35, 95% CI 0.63 to 2.88), but the difference was not significant (*see Table 17*). The risk was significantly higher for the overweight and obese categories than for the healthy weight category (overweight: fully adjusted OR 4.0, 95% CI 1.69 to 9.58; obese: fully adjusted OR 3.29, 95% CI 1.20 to 8.99). Those in the underweight category were less likely to gain excessive gestational weight than those with a healthy weight but this was not significant (fully adjusted OR 0.57, 95% CI 0.06 to 5.31). In sensitivity analyses, when adjusted for the effect of baby's weight and rates of smoking abstinence, the mean difference in the weight change between the two groups was slightly changed and the effect of baby's weight was significant in the regression models (*see Table 17*).

TABLE 17 Comparison of maternal weight change (kg) between early pregnancy and the end of pregnancy (separate analysis for subsamples providing maternal weight before and after delivery) by randomisation group

Variable	PA group ($n = 74$), mean (SD)	Control group ($n = 66$), mean (SD)	Basic adjustment, mean difference PA vs. control (95% CI);[a] *p*-value	Fully adjusted, mean difference PA vs. control (95% CI);[b] *p*-value
***Subsample at end of pregnancy with maternal weights measured before birth* (n = *140*)**				
Early pregnancy weight	68.3 (14.4)	70.3 (15.6)		
EOP weight	80.7 (14.9)	81.4 (14.7)		
Weight change	12.4 (6.1)	11.2 (7.0)	1.08 (–1.08 to 3.23); 0.325	0.92 (–1.15 to 2.99)
				0.99 (–0.98 to 2.95)[c]
Weight change per gestational week	0.31 (0.15)	0.27 (0.17)	0.04 (–0.01 to 0.10);[d] 0.113	0.02 (–0.03 to 0.08);[e] 0.449
				0.02 (–0.04 to 0.08);[c,e] 0.555
	PA group ($n = 74$), *n* (%)	**Control group ($n = 66$), *n* (%)**	**OR adjusted for centre (95% CI);[f] *p*-value**	**Fully adjusted OR (95% CI);[g] *p*-value**
Excessive gestational weight relative to early pregnancy BMI	30 (40.5)	24 (36.4)	1.26 (0.63 to 2.53); 0.520	1.35 (0.63 to 2.88); 0.440
				1.36 (0.60 to 3.09);[c] 0.456
	PA group ($n = 63$), mean (SD)	**Control group ($n = 68$), mean (SD)**	**Basic adjustment, mean difference PA vs. control (95% CI);[a] *p*-value**	**Fully adjusted, mean difference PA vs. control (95% CI);[b] *p*-value**
***Subsample at end of pregnancy with maternal weights measured after birth* (n = *131*)**				
Early pregnancy weight	66.1 (14.6)	66.2 (13.8)		
EOP weight	70.7 (14.1)	71.3 (13.4)		
Weight change	4.7 (7.2)	4.9 (7.3)	–0.11 (–2.27 to 2.49); 0.928	–0.25 (–2.59 to 2.09)
				–0.19 (–2.53 to 2.15)[c]

EOP, end of pregnancy.

a Linear regression model with maternal weight change at EOP as the dependent variable and randomisation groups, early pregnancy weight and recruitment centre as independent variables.

b In multiple linear regression models, adjusted for randomisation groups, early pregnancy weight, recruitment centre, age, number of previous pregnancies and weight at early pregnancy.

c Sensitivity analysis: in all analyses, further adjustment for continuous smoking abstinence at EOP and baby's weight. Sample sizes for these analyses are $n = 134$ (subsample providing maternal weight before birth) and $n = 127$ (subsample providing maternal weight after birth) because of missing data for baby's weight and the exclusion of twin births.

d Multiple linear regression analysis with maternal weight change (kg) per gestational week at EOP as the dependent variable, and randomisation groups and recruitment centre as independent variables, ($n = 132$).

e Multiple linear regression analysis with maternal weight change (kg) per gestational week at EOP as the dependent variable and randomisation groups, early pregnancy obesity, interaction between randomisation groups and early pregnancy obesity, recruitment centre, age and number of previous pregnancies as independent variables, ($n = 132$).

f Logistic regression model with excessive gestational weight relative to early pregnancy BMI (yes/no) as the dependent variable and randomisation groups as the independent variable.

g Adding BMI categories at early pregnancy (healthy weight, underweight, overweight and obese) to the above model and adjusting for age and number of previous pregnancies.

Chapter 4 Health economic analysis and results

Introduction

Several studies have investigated the potential cost saving of smoking cessation interventions in pregnancy[92] but only one study could be identified that has used empirical data on costs to calculate the incremental cost-effectiveness of these interventions.[93] This chapter reports on an economic evaluation conducted alongside the LEAP trial to address the cost-effectiveness of a PA intervention plus behavioural support compared with behavioural support alone.

The objectives were:

1. to compare the costs associated with the control and intervention strategies
2. to estimate the consequences of these alternatives
3. to assess the cost-effectiveness of the PA intervention used in addition to behavioural support for smoking cessation at the end of pregnancy.

Methods

Overview

A cost-effectiveness analysis was undertaken to compare a PA intervention plus behavioural support with behavioural support only for women who were smoking in pregnancy. The main outcome for the economic evaluation was biochemically validated abstinence from smoking between a quit date and the end of pregnancy. As recommended by the National Institute for Health and Care Excellence (NICE),[94] a cost–utility analysis with a fully incremental analysis was conducted from a NHS and personal social services viewpoint, including direct health effects (maternal smoking cessation) and costs (or cost savings) to the NHS. Women were eligible for inclusion in the trial if they were between 10 and 24 weeks' gestation and outcomes were collected at the end of pregnancy (between 36 weeks' gestation and 10 weeks post partum); therefore, the time horizon of the trial was up to 9 months. A clinical trial of NRT for smoking cessation (Smoking, Nicotine, and Pregnancy; SNAP)[95,96] was approved by the NIHR HTA programme shortly before this study began and, as both studies used similar outcome measures, a similar approach has been taken to economic evaluation to permit comparison.

Cost estimation

Two main costings were included: first, the costs of the interventions and, second, the costs of caring for each woman and her infant during the period between randomisation and the immediate postnatal period (up to 6 weeks post partum).

Intervention costs

The cost of the interventions included training and time for staff to deliver the behavioural support and PA consultations (costed as Band 6 midwife, including overheads) as well as equipment and consumable costs [CO monitors (breath testing equipment), consumables associated with CO breath testing, equipment (treadmills and pedometers to count steps when walking), exercise DVDs, printing of PA manual for participants], and childcare costs. Participants in both arms were offered up to six sessions of behavioural support for smoking cessation. In addition, those in the PA arm were offered 14 sessions of supervised treadmill exercise and nine PA consultations, which were combined with the smoking cessation support. All of the support was provided face to face. The time spent providing support in the trial was multiplied by salary and overhead costs to calculate a cost per session.

The cost per use of CO monitoring in the trial was calculated by first summing the costs of equipment and consumables and then dividing the total cost by the total number of uses. The equipment and consumables included 12 CO monitors [two calibration kits, semi-disposable mouth pieces (assuming that these were changed every 60 uses), batteries (assuming that these were changed every 210 uses) and additional mouth pieces per each use (used in combination with semi-disposable mouth pieces)] and alcohol-free wipe per use. Assumptions concerning the need to change semi-disposable mouth pieces and batteries were taken from the SNAP trial.[96]

It was assumed that a treadmill would last for 10 years and that three midwives would require training in that time; therefore, annual costs were calculated as one-tenth of the cost of a treadmill plus one-tenth of the cost of training three midwives, calculated as 1 day of PA training and 1 day of smoking cessation training received by each midwife. The costs of training were derived from the costs of training in the LEAP trial. In the control arm, only the cost of smoking cessation training was included. A professor of clinical psychology provided the smoking cessation training and a private PA consultant, specialising in exercise and pregnancy, delivered the PA training; both of these trainers regularly provide training in the NHS.

We wanted to present findings for an 'average/typical' hospital and so made the following additional assumptions: given a hospital with 5000 births per year with 600 (12%) pregnant smokers (based on national data)[7] and using the recruitment rate in the LEAP trial of 9.7% (785/8096 eligible women randomised), 58 (9.7% of 600) women would be recruited annually per hospital. Therefore, per-participant costs for the treadmill and training were estimated by dividing the annual costs by 58. The robustness of the results to this assumption was tested in sensitivity analysis.

Health-care resource use costs

Information about antenatal and postnatal hospital admissions and mode of delivery was collected from maternal medical records and data on admissions to neonatal special care came from infant medical records.

Valuation of costs

All data were valued in monetary terms and unit costs were reported in UK pounds for the financial year 2012/13 (representing the end point of the trial). As follow-up did not continue beyond 9 months post randomisation, the question of discounting future costs did not arise. For standard NHS health care, UK unit costs were applied from national sources, increasing the generalisability of the results. *Table 18* presents a summary of the resource use and unit costs.

Calculating costs

To calculate the cost of face-to-face support for each trial participant we multiplied the number of treatment sessions by the duration of support in minutes. For the PA group we assumed that the midwife engaged with the woman only when she was off the treadmill, except that during the first 5 minutes of each treadmill walking session the midwife provided some PA counselling; the estimate of 5 minutes is based on interviews with the researchers who provided the interventions. Besides these 5 minutes, for the rest of the time that the woman was on the treadmill the midwife was able to proceed with her normal work.

Example

Suppose that a patient has 11 treatment sessions lasting 471 minutes (including treadmill time) and uses the treadmill in 10 of these sessions for a total of 279 minutes. This patient will have spent $471 - 279 = 192$ minutes in treatment sessions when not using the treadmill. It is assumed that the midwife contact time consists of these 192 minutes plus a further 5 minutes for each of the 10 sessions in which a treadmill was used. Total midwife time is therefore $(471 - 279) + (10 \times 5) = 242$ minutes.

TABLE 18 Unit costs (2012/13 prices)

Resource item	Unit cost (£)	Unit	Source
PA group only			
Treadmill	775	Per treadmill	LEAP trial estimation
Pedometer	7.12	Per pedometer	LEAP trial estimation
Printing	0.58	Nine-page PA manual	LEAP trial estimation
Exercise DVD	0.80	Per DVD	LEAP trial estimation
PA training costs	120	Per midwife trained	LEAP trial estimation
Both groups			
Smoking cessation training	250	Per midwife trained	LEAP trial estimation
Band 6 (midpoint) midwife time (including overheads)	31.95	Per hour	Curtis[97]
CO monitors and consumables	1.37	Per use	LEAP trial estimation
Childcare	15	Per crèche visit	LEAP trial estimation
Health-care use (both groups)			
Maternal antenatal admission	582.24	Per day	Department of Health[98]
Mode of delivery			
Unassisted vaginal delivery	2313.60	Per obstetric delivery	Department of Health[98]
Assisted vaginal delivery	2788.86		
Caesarean section	3848.83		
Miscarriage	1376.76		[a]Petrou *et al.*[99]
Baby admission to neonatal unit (assumes an average of 4 days in hospital)	2967.18	Per admission	Department of Health[98]
Maternal postnatal admission	782.68	Per day	Department of Health[98]

a Average NHS cost of miscarriage management inflated to 2012–13 prices using the Hospital and Community Health Services Pay and Price Index.[97]

Note

To calculate the cost of a baby's admission to neonatal care, a weighted average of bed-day costs for neonatal critical care taken from NHS reference costs was multiplied by a weighted average length of stay for neonates with major diagnoses derived from Hospital Episode Statistics for 2012–13.[98] The daily costs of antenatal and postnatal admissions were established by calculating a weighted average of daily unit costs of different health-care resource group activities recorded in NHS reference costs.[98] For settings with a length of stay longer than 1 day, information on bed-days was used to calculate a weighted average daily cost. Quantities of services used were multiplied by the relevant unit costs to estimate overall cost profiles for women in the trial.

The cost of mode of delivery was established by calculating a weighted average of unit costs for different modes of delivery activities recorded in NHS reference costs.[98] A similar method was used to calculate an average cost of a maternal antenatal admission and postnatal admission, based on antenatal observations and investigations.

Outcome measure

The measure of health benefit for the economic evaluation was the same as the primary measure of clinical effectiveness in the LEAP trial: self-reported and biochemically validated maternal smoking cessation from the quit date to the end of pregnancy. Temporary smoking lapses of up to a total of five cigarettes (on up to five occasions) were permitted.

Analysis

An incremental cost-effectiveness analysis was undertaken, following the NICE guidance for health-care evaluations,[94] comparing the additional costs of a PA intervention with those of behavioural support alone, as well as the additional benefits, to give a cost per additional quitter.

Results are first presented as the per-participant quit rate and costs including fixed costs apportioned as described earlier in *Cost estimation*. The same results have also been scaled up to the expected annual costs and outcomes for a typical hospital with 58 participants per year as used for the estimation of fixed costs.

When two interventions are compared in a cost-effectiveness analysis it may be the case that the more effective intervention is also the less costly. In this case, the strategy that is both more effective and less costly is said to *dominate* the other strategy. The dominating strategy is then unconditionally preferred regardless of any considerations of budget. When no dominance relationship exists, the results are summarised in the incremental cost-effectiveness ratio (ICER), which is the additional cost of achieving one extra quitter. It can be calculated as the expected per-participant cost of the intervention group over and above that of the control group divided by the expected difference in quit rate. The following is the formula for the ICER, where Δ represents change, C represents the costs, E represents the effects and subscripts I and C refer to the intervention and control respectively:

$$ICER = \frac{\Delta C}{\Delta E} = \frac{C_I - C_C}{E_I - E_C}. \quad (1)$$

(Note that when a dominance relationship exists, the ICER as calculated above is negative, but the numerical value is not informative. This can be seen because doubling either ΔC or ΔE makes the dominance relationship stronger but these two possible changes have opposite effects on the numerical value of the ICER.)

A total of 785 women were included in the primary ITT analysis, 392 in the PA group and 393 in the control group. However, one individual in the PA group withdrew consent before providing any data or receiving any treatment and was therefore excluded from the economic evaluation. Thus, we analysed data for 391 in the PA group and 393 in the control group. Analyses were conducted in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA).

There were no missing data for the effectiveness outcome (validated smoking cessation from quit date to the end of pregnancy) as any women without validated smoking cessation data were assumed to be smokers. The average resource use of each cost item was estimated from the available data for the relevant arm of the trial, effectively imputing an average for each woman with missing data. This was justified following preliminary analysis, which showed no significant association between any of the resource use items and key patient baseline characteristics associated with smoking cessation (age, FTCD score, EPDS score, partner's smoking status, age leaving full-time education) plus quit status at the end of pregnancy. Age was significantly associated with mode of birth, such that those who were older were

more likely to have a caesarean section. In addition, those with a higher EPDS score were significantly more likely to report at least one antenatal hospital admission and one postnatal admission. However, as neither age nor EPDS score was significantly associated with smoking status at the end of pregnancy, these associations with resource use were not considered a concern when imputing missing data.

Bootstrapping was used to assess the joint uncertainty in cost and effectiveness outcomes. Missing data were imputed individually for the relevant resource use items to produce a complete data set. Bootstrapped data sets of the same size as the original patient groups were then constructed by sampling at random with replacement. Incremental cost and effectiveness estimates were then calculated using the same methods as described earlier. This was repeated 2000 times to produce a joint distribution of incremental costs and effectiveness, which was plotted on a cost-effectiveness plane.[100] A cost-effectiveness acceptability curve[101] was generated showing the proportion of bootstrapped replications that would be cost-effective at a range of threshold ICERs.

The baseline characteristics of age and nicotine dependence are reliable predictors of smoking cessation. Therefore, in a subgroup analysis, cost-effectiveness calculations were repeated using only data for the following subgroups: women aged < 28 years, women aged > 27 years, women with a FTCD score of < 4, women with a FTCD score of ≥ 4.

Results

In the PA group 30 of 391 women (7.7%) were abstinent from smoking with biochemical validation from the quit date to the end of pregnancy; the equivalent figure for the control group was 25 of 393 women (6.4%), a non-significant difference (*see Chapter 3, Results*).

Table 19 reports the health-care resources utilised in the two arms of the trial. Quantities of services were multiplied by the relevant unit costs in *Table 18* to calculate the resource use for each woman. Maternal antenatal and postnatal hospital admissions and admissions to neonatal care were similar in the two groups. With regard to mode of birth, the PA group underwent more assisted and spontaneous vaginal births and the control group underwent more caesarean sections and miscarriages. A chi-squared test including all four modes of birth showed a significant difference between the groups ($\chi^2 = 8.7$, $p < 0.035$). On average, the PA group attended 5.3 of 14 treatment sessions offered and the control group attended 3.5 of six sessions offered. The total duration of treatment sessions was around twice that for the PA group compared with the control group.

The point estimate results shown in *Table 20* suggest that the PA intervention is somewhat less costly than the control intervention, by a margin of £35 per participant, but produces a small increase in the expected number of quitters. Taken in isolation, this suggests that the PA intervention should be adopted, regardless of the decision-maker's willingness to pay for an additional quitter. However, this result must be interpreted with great caution because there is considerable statistical uncertainty, as reflected in the scatterplot (*Figure 5*), which shows that neither the cost difference nor the effect difference is statistically significant as there are an appreciable number of points in each quadrant. This is confirmed by the cost-effectiveness acceptability curve (*Figure 6*), which shows that the proportion of bootstrapping replications deemed cost-effective does not exceed 80% for any willingness-to-pay threshold up to £50,000 per additional quitter.

The 'stripey' effect in the cost-effectiveness scatterplot (*see Figure 5*) reflects the discrete nature of the outcome measure. One additional quitter selected in the bootstrapping moves the point to the next stripe. It appears that the estimated cost saving from the PA intervention is driven by the increased use of health-care resources in the control group, particularly with regard to the rate of caesarean section.

TABLE 19 Health-care resource utilisation

Resource item	PA group ($n = 391$)	Control group ($n = 393$)
Maternal antenatal hospital admissions[a]		
Missing data, *n/N* (%)	46/391 (11.8)	56/393 (14.2)
Admissions, *n/N* (%)	85/345 (24.6)	72/337 (21.4)
Average length of days per admission, mean (SD)	2.9 (10.5)	2.3 (2.5)
Baby admitted to neonatal unit, *n/N* (%)[a]		
Missing data	31/391 (7.9)	35/393 (8.9)
Admissions	29/360 (8.1)	36/358 (10.1)
Maternal postnatal hospital admissions[a]		
Missing data, *n/N* (%)	36/391 (9.2)	42/393 (10.7)
Admissions, *n/N* (%)	275/355 (77.5)	271/351 (77.2)
Average length of days per admission, mean (SD)	2.1 (1.6)	2.2 (1.9)
Mode of birth, *n/N* (%)		
Missing data	20/391 (5.1)	22/393 (5.6)
Assisted vaginal birth[b]	49/391 (12.5)	33/393 (8.4)
Caesarean section	77/391 (19.7)	104/393 (26.5)
Spontaneous vaginal birth	239/391 (61.1)	224/393 (57.0)
Miscarriage	6/391 (1.5)	10/393 (2.5)
Number of treatment sessions, mean (SD)	5.3 (4.1)	3.5 (1.9)
Total duration of treatment sessions (minutes), mean (SD)	177.3 (146.0)	86.8 (51.2)
Number of sessions using treadmill, mean (SD)	4.9 (4.0)	NA
Total time on treadmill (minutes), mean (SD)	93.3 (92.2)	NA
Number of crèche sessions,[c] mean	0.46	0.22

NA, not applicable.
a The average length of stay is shown for maternal admissions, for which a unit cost per day has been applied. For neonatal admissions the unit cost is per admission and so length of stay is not needed.
b For three sets of twins the first baby had a spontaneous birth and the second had an assisted birth. In these cases the resource use for the mother was counted as assisted.
c A crèche was available at only four of 13 hospital sites and the mean has been calculated across all patients; therefore, in this case reporting the SD is not relevant.

TABLE 20 Results of the incremental cost-effectiveness analysis

Group	Average per-participant intervention cost (£, 2012/13 prices)	Average per-participant resource use cost (£, 2012/13 prices)	Average per-participant cost (£, 2012/13 prices)	Quit rate (%)	Expected annual cost[a] (£, 2012/13 prices)	Expected annual quitters[a]	ICER
PA	83	4630	4713	7.7	273,343	4.45	Not calculated: PA dominates the comparator in the point estimate result
Control	56	4692	4748	6.4	275,373	3.69	
Difference	27	–62	–35	1.3	–2029	0.76	

a Expected annual costs and number of quitters based on 58 participants per year.

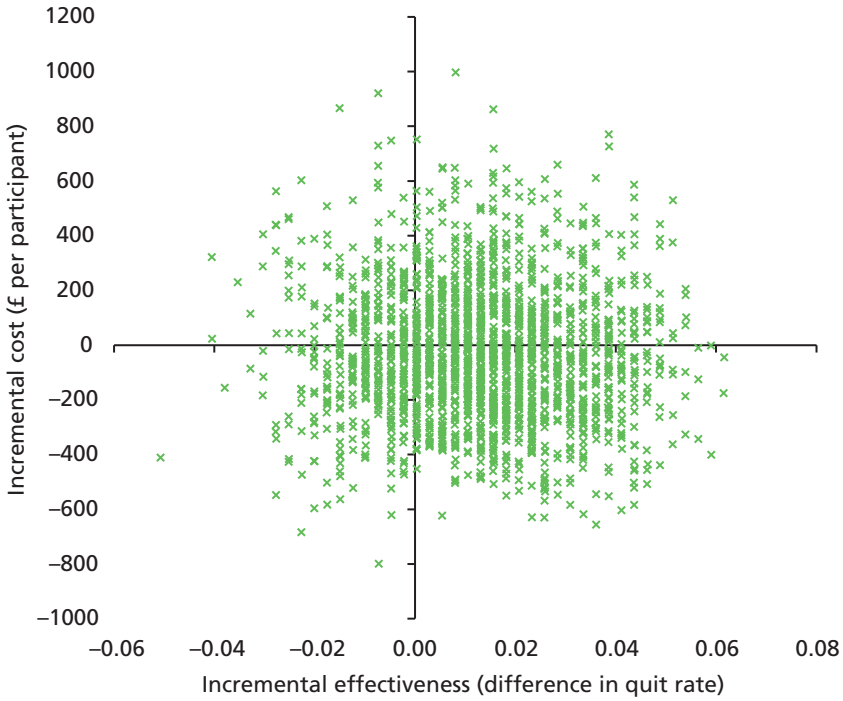

FIGURE 5 Cost-effectiveness scatterplot.

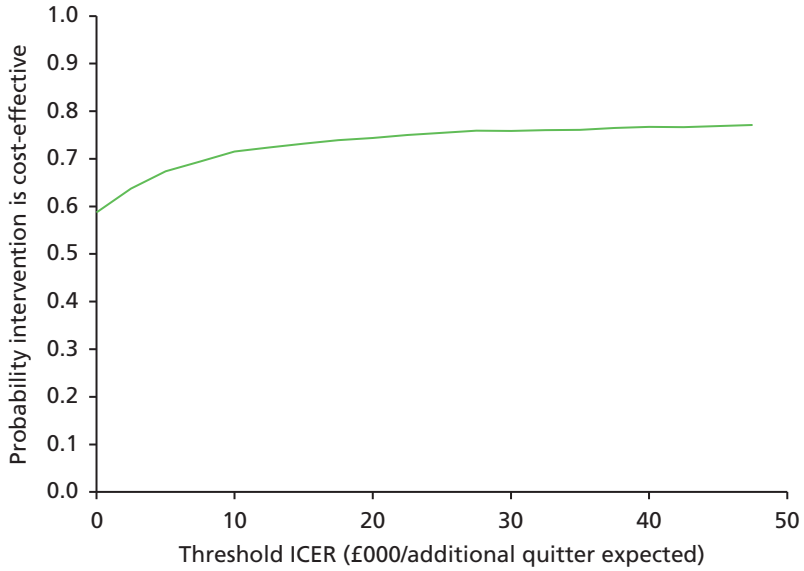

FIGURE 6 Cost-effectiveness acceptability curve.

The results were calculated assuming that the costs for treadmill and midwife training would be based on a typical hospital size. The effect of these costs is negligible compared with other costs in the analysis and so varying this assumption makes no appreciable difference to the results. *Table 21* presents illustrative results showing the effect on overall costs and the difference in costs of two possible scenarios. In the first scenario the per-participant fixed costs were halved, assuming that the treadmill and training would apply to twice as many participants (116 per year instead of 58). In the second scenario the per-participant fixed costs were doubled, assuming that the treadmill and training would apply only to half as many participants (29 per year).

TABLE 21 Sensitivity analysis for assumption about handling fixed costs

Scenario	Average cost per participant (£, 2012–13 prices)		
	PA group	Control group	Difference
Base case	4713	4748	–35
Halve per-participant fixed costs	4711	4747	–36
Double per-participant fixed costs	4716	4749	–33

In a subgroup analysis, when repeating the calculations for the two categories of age and FTCD score, the point estimates no longer show PA dominating the control, but the bootstrapped results still occupy all four quadrants of the cost-effectiveness plane and, thus, it cannot be concluded that the intervention is cost-effective (or not) for any of these subgroups. Further details of the subgroup analysis are provided in *Appendix 10*.

Summary

Costs associated with the control and PA interventions were compared and the consequences of these alternatives were estimated. The main results of the cost-effectiveness analysis can be summarised as follows:

- Mean costs were £35 per participant lower in the PA group than in the control group. This results from the fact that the mean intervention costs were £27 higher in the PA group than in the control group but health-care resource use costs were £62 higher in the control group. An important contributory factor to this result was the difference in rates of caesarean section (25% control group vs. 19.7% PA group).
- Taken in isolation, the reduction in mean costs and increase in quit rate suggest that the PA intervention should be adopted, regardless of the decision-maker's willingness to pay for an additional quitter. However, this result must be interpreted with great caution because there is considerable statistical uncertainty, as reflected in the scatterplot and accompanying cost-effectiveness acceptability curve.
- Subgroup analysis was performed by age and dependency score. In each subgroup analysis there was still considerable uncertainty in both the incremental costs and the difference in quit rate.

Chapter 5 Discussion

Smoking outcomes

The trial showed that, among women who were recruited at 10–24 weeks of pregnancy, supplementing behavioural support with a PA intervention was no more effective than behavioural support alone in promoting smoking cessation at the end of pregnancy. At this time, the self-reported continuous smoking abstinence rate, with biochemical validation, was 1.3% higher among those in the PA group than among those in the control group, but this difference was not statistically significant.

Strengths and limitations

This is the first trial to assess the effect of a PA intervention on smoking cessation during pregnancy. Limitations of previous trials of PA interventions for smoking cessation were overcome[22] through offering an intensive PA intervention (with support to increase PA as an aid for smoking cessation in addition to supervised exercise sessions), assessing and validating PA in both groups, using a robust outcome of continuous smoking abstinence and offering a pragmatic intervention that could be readily integrated into routine health care in the NHS.

This study was approximately twice as large as previous RCTs investigating PA interventions for smoking cessation delivered via face-to-face support.[22] As anticipated, around 10% of pregnant women recorded as smokers at their first antenatal booking visit were recruited. However, the overall number of women recorded as smokers was lower than anticipated; therefore, despite extending the recruitment period, we recruited only 91% of the target population of 866 (i.e. $n = 789$). Future studies may wish to aid recruitment by focusing on regions of the UK that have particularly high rates of smoking in pregnancy. Quit rates were lower than anticipated in our power calculation, which will also have reduced the power of the study. The CI around the OR for the effect of the intervention shows the level of precision of this estimate, given the achieved sample size, and implies that we cannot rule out up to a twofold increase in abstinence at the end of pregnancy in the intervention group compared with the control group at the upper end of the CI, although our point estimate suggests an effect of the intervention that is unlikely to be clinically meaningful. Additionally, at the 4-week follow-up point quit rates were higher and CIs narrower, and the difference in abstinence between the treatment group and the control group was minimal, even at the upper end of the CI. Thus, despite not reaching the target sample size, our results suggest that there is unlikely to be a clinically relevant difference between the groups. Quit rates were lower than in previous pregnancy trials with less rigorous outcome measures but were similar to those in studies using comparable outcome measures.[12] For example, two previous UK-based large trials of a smoking cessation intervention during pregnancy observed quit rates at the end of pregnancy of 7.6% and 7.8% in a group receiving only behavioural support for smoking;[95,102] similarly, we observed a quit rate of 6.4% for this group.

Our finding of a lack of an effect of a PA intervention on smoking abstinence is consistent with most previous trials of PA for smoking cessation among non-pregnant smokers. However, these trials had low statistical power or used insufficiently intense interventions.[22] One adequately powered trial showed that regular, supervised, vigorous-intensity PA was effective for smoking cessation in women.[23] However, such an intensive intervention is not likely to be clinically suitable or appealing to most pregnant smokers and our finding remains that a pragmatic intervention based on moderate-intensity exercise was not effective for aiding smoking cessation during pregnancy.

Secondary outcomes

Cigarette withdrawal symptoms and urges to smoke

Reports of cigarette withdrawal symptoms and urges to smoke are important during smoking cessation as they predict relapse to smoking; pharmaceutical interventions are thought to largely work through reducing these symptoms.[18] There was no evidence of the PA intervention affecting changes in withdrawal symptoms or urges to smoke, rated for the last week, between baseline and 1 week of abstinence. The ratings for all of the withdrawal symptoms were fairly low at baseline (mean score 2.3, scale 1–5) and there may have been a floor effect for these items. The lack of a PA effect on cigarette withdrawal or urges to smoke is inconsistent with studies showing that brief bouts of PA have an acute effect on reducing urges to smoke among non-pregnant smokers[21] and pregnant smokers.[29] However, these studies included temporarily abstinent smokers and findings from this study are likely to have more clinical relevance. It is possible that, among women attempting to stop smoking, bouts of PA have acute beneficial effects on reducing the urge to smoke but that these do not translate into benefits that extend across the week.

Confidence for participating in physical activity and stopping smoking

Increased confidence for participating in PA and stopping smoking (i.e. self-efficacy) tends to predict positive changes in these behaviours[103,104] and, if the PA intervention has the potential to aid smoking cessation, we might expect it to increase self-efficacy in both of these domains. There was a significant difference in self-efficacy for PA between baseline and 1 week for the two groups; however, the difference was a modest 0.3 (scale 1–5) and was the result of scores remaining unchanged in the PA group and scores reducing (i.e. reduction in self-efficacy) in the control group. The difference in scores for self-efficacy for smoking cessation between baseline and 1 week was 0.2 (scale 1–6), which was not statistically significant. Thus, there was little evidence to show that the intervention positively influenced these processes.

Birth outcomes

Maternal and fetal birth outcomes were very similar between the two study groups, except that there were significantly fewer deliveries by caesarean section in the PA group than in the control group (difference of 7%). The finding of a lower incidence of caesarean sections in the PA group is consistent with the results of a recent meta-analysis of RCTs showing a significantly lower risk of caesarean delivery among women undergoing a PA intervention compared with a control group.[47] Ours is the first study to report this in pregnant smokers and it is a positive result as caesarean sections are more expensive to the NHS than other modes of delivery and there are complications associated with abdominal surgery. It has been hypothesised that this effect may be related to reduced birthweight or maternal weight in a more physically active group.[47] In the meta-analysis maternal weight, but not birthweight, was significantly reduced in the PA groups compared with the control groups, although for most of the individual studies either maternal weight was not measured or there was no significant reduction in weight. In the one study reporting a significantly lower risk of caesarean delivery among women undergoing a PA intervention compared with a control condition, maternal weight was not reported. Therefore, there is as yet no evidence to support either of these hypotheses. Moreover, in the current study neither maternal weight nor birthweight was significantly influenced by the intervention and so these are unlikely as explanations. There may be another mechanism operating, for example it is possible that more active women have more efficient uterine contractions and therefore are more likely to avoid caesarean section. Further studies are needed to replicate this finding and to explore underlying mechanisms.

Adverse events

There were similar numbers of AEs and SAEs in the two study groups and there were only two AEs potentially related to the PA intervention. This is reassuring as it suggests that a PA intervention is safe and is unlikely to increase these events in pregnant smokers.

Maternal weight

There was no evidence that randomisation led to reduced weight gain overall or reduced the tendency to gain excessive weight during gestation. Obesity did not modify the association between trial arm and weight gain.

The subsample of the LEAP participants included in the analysis of maternal weight study were much more likely to have stopped smoking than those who were not included. This was because abstinent participants had to return for biological confirmation of abstinence and they were obviously keen to return to show their success. Weighing participants was then possible. Although this is of some concern, it is a much less relevant concern here than it might appear. Post-cessation weight gain occurs only in those who sustain abstinence and therefore there is no potential for PA to ameliorate cessation-related weight gain in those not achieving abstinence. Consequently, the Cochrane review[48] of interventions to prevent cessation-related weight gain confines the analysis to only participants who achieve abstinence in the intervention and control arms.

Pregnancy itself is a period when excessive weight gain occurs commonly, as shown in this trial, in which 38% of women gained an excessive amount of weight. PA might have been expected to ameliorate this, but there was no evidence it did so. The CIs were wide and encompassed modest effects that are clinically relevant. We can therefore conclude only that the PA programme had no large effects on GWG but may still have important, moderate-sized effects, although there is insufficient evidence to assess this.

Maternal depression

The PA intervention was no more effective than standard behavioural support for reducing depression scores at the end of pregnancy or 6 months after childbirth. Moreover, scores were significantly higher in the PA group than in the control group at the end of pregnancy, although the margin of this difference was very small and is unlikely to be clinically important.[105,106] AEs were very similar in the two groups and so this is unlikely to have affected this outcome. As for the smoking outcomes, there may have been limited potential to show a difference between the groups as both groups were already active at baseline and reported maintaining fairly high levels of PA through to the end of pregnancy. That said, the self-reported PA must be treated with caution as the accelerometer data suggest that these reports were overestimated and, among the sample with accelerometer data, levels of activity were similar for the two groups.

Another explanation for the findings relates to the population of interest and the requirements of the study/intervention. Those in the PA group were asked to change two health behaviours simultaneously (i.e. PA and smoking) while also coping with being pregnant, in addition to dealing with the demands of being asked to attend multiple treatment sessions. This might have demoralised these individuals and they may have found this difficult to achieve, resulting in marginally higher depression scores at the end of pregnancy.

In conclusion, although clinical guidelines recommend that pregnant women exercise for mental health benefits[28,61,107] and there is a further recommendation that PA be used to treat and prevent depression among smokers,[108] based on the current findings an intervention that offers supervised exercise combined with consultations to increase PA cannot be recommended for antenatal or postnatal depression in women attempting to quit smoking during pregnancy.

Economic evaluation

The total mean cost was £35 per participant lower in the PA group than in the control group. This results from the mean health-care resource use costs being £62 higher in the control group than in the PA group and the mean intervention costs being £27 higher in the PA group than in the control group. Control group health-care costs were higher mostly because of the higher rate of caesarean sections in this group (25% control group vs. 19.7% PA group). Considering the reduction in mean cost and increase in quit rate for the PA group compared with the control group, it could be recommended that the PA intervention be used as

an aid for smoking cessation regardless of the decision-maker's willingness to pay for an additional quitter. However, these results must be interpreted with extreme caution as there is considerably statistical uncertainty, as reflected in the scatterplot and accompanying cost-effectiveness acceptability curve.

Previous studies have investigated the cost-effectiveness of smoking cessation interventions during pregnancy.[92] However, these mainly US-based studies are limited by not including data for infant outcomes and therefore cannot easily be compared with this study. One previous study (the SNAP trial[96]), based in the UK, has considered infant outcomes and conducted a similar analysis as used in the present study. The SNAP trial assessed the cost-effectiveness of NRT for smoking cessation. The authors reported that the total mean cost of the intervention was £90.81 higher in the NRT group than in the usual-care group. While bearing in mind the high levels of statistical uncertainty present in both studies, this suggests that the PA intervention may be at least as cost-effective, if not more so, than the NRT intervention.

The National Institute for Health and Care Excellence recommends that health outcomes should be measured in quality-adjusted life-years (QALYs) to facilitate comparisons between different health-care programmes.[94] Ideally, the value to society of each successful quitter in the LEAP trial would be estimated in QALYs but no method has been found for doing this that can be considered robust and reliable for use with pregnant smokers. QALYs are commonly calculated from generic health-related quality of life tools (e.g. the European Quality of Life-5 Dimensions or EQ-5D), which may be inappropriate for use in pregnant populations. Quality-of-life studies using generic measures have demonstrated that changes in quality of life, particularly declining physical functioning and vitality, occur over the course of pregnancy.[109] These substantial changes in quality of life may mask any potential short-term quality-of-life gains from smoking cessation. Moreover, existing models ignore QALY benefits to the fetus and do not take into account maternal morbidity during pregnancy.[92,93,110] It was anticipated that a model and systematic review being developed for another study at the University of Nottingham would be suitable for this purpose but this work has yet to be completed. However, once an appropriate economic model that values smoking in pregnancy is available we will use this to estimate cost-effectiveness in QALYs.

Interpretation and generalisability of the results for smoking outcomes

The trial had reasonably broad inclusion criteria and few exclusion criteria, and, therefore, the results are likely to be generalisable to most pregnant smokers, although the women were highly physically active in both groups at baseline. At baseline, compared with a survey of pregnant smokers similarly recruited in antenatal hospitals,[111] participants were approximately twice as likely to report achieving the recommended 150 minutes per week of MVPA; this may be because more active women were attracted to a trial offering a PA intervention. Low attendance may have affected efficacy, with the PA group attending a median of only four (of 14) sessions. Low attendance was not explained by the two potentially treatment-related AEs in the PA group and there was no indication that the PA intervention increased the overall incidence of AEs. The vast majority of women who failed in their quit attempt stopped attending, suggesting that it was failure to quit that led to low attendance rather than low attendance leading to failure of the attempt. There was no evidence for the intervention influencing processes that might aid cessation, such as confidence for quitting, urges to smoke or withdrawal symptoms.

Bias in outcome ascertainment is unlikely to explain the findings as follow-up rates were equally high in the groups and the effect size was independent of the influence of missing outcome data. Fewer than 10% of participants reported using non-study behavioural support or NRT, with similar usage in the groups. Therefore, it is doubtful that this influenced the results.

Although the intervention group reported significantly higher PA levels throughout pregnancy relative to the control group, the self-reported PA scores in the control group were also relatively high at follow-up. For example, at the end of pregnancy the intervention group reported completing a median of

155 minutes of MVPA per week (22 minutes per day) and the control group reported completing a median of 140 minutes of MVPA per week (20 minutes per day). This suggests that some intervention contamination might have occurred in the control group and consequently there was an insufficient difference in PA levels between the groups to show an appreciable effect on depression outcomes. It is not clear why the control group participated in more PA than might be expected. One explanation could be that an atypical motivated sample of participants was recruited who were keen to be active regardless of their random group allocation; the high baseline PA scores would suggest this explanation is a possibility as participants were already achieving around 30 minutes per day of MVPA at baseline. The only previous trial of exercise for smoking cessation showing a long-term benefit for abstinence excluded more active women,[23] and in less active women the LEAP intervention might have had more positive effects. However, there was no evidence to suggest that the treatment effect for the primary outcome was influenced by baseline levels of PA. Moreover, as participants were recruited from routine health-care settings, it seems likely that if the exercise intervention was offered as part of routine care women would be recruited who are active at a similar level to those taking part in the current trial.

It is also important to consider that, as previously observed,[112–114] our accelerometer correlational analysis and Bland–Altman plot suggest that participants overestimated their self-reported PA levels. Moreover, participants could not be blinded to treatment allocation and the higher self-reported rates of activity in the PA group may be the result of a social desirability bias, such that there is a tendency to over-report PA levels with the belief that this will be positively viewed by the researchers. In addition, in the subsample using the accelerometer, accelerometer-derived PA levels were similar in the two trial groups, although when including all MVPA (rather than restricting it to bouts of > 10 minutes) the PA group tended to report more PA per week than the control group, which suggests that most increases in activity were likely to be in sporadic bouts lasting < 10 minutes. The accelerometer data were collected for only 10% of participants and therefore this finding must be treated with caution; however, it is possible that the non-significant effects for smoking abstinence emerged partly because the PA group failed to adhere fully to the behavioural goals of the intervention. If this is the case, it is unlikely that such an intervention offered in routine health care would raise PA levels sufficiently to have an impact on smoking cessation. On the other hand, although attendance at treatment sessions was low, the PA counselling may have increased PA even without attendance at all scheduled exercise sessions. A less pragmatic and more efficacy-oriented trial (e.g. with greater incentives to complete the exercise, such as financial incentives) with accelerometer measurement in the whole sample would be needed to establish whether or not PA per se aids smoking cessation during pregnancy.

Conclusion

During pregnancy, offering an intervention combining supervised exercise and PA counselling did not add to the effectiveness of behavioural support for smoking cessation. There was no evidence that the PA intervention increased AEs or had a harmful effect on birth outcomes, and there was some evidence that the PA intervention resulted in fewer caesarean sections. There was no evidence for the intervention reducing maternal depression or weight gain.

Recommendations for research (in priority order)

1. It is not recommended to fund further large-scale trials of PA for smoking cessation until much less expensive observational studies have been conducted to provide promising leads, for example related to the populations most suitable for such interventions and methods for increasing PA adherence.
2. Reasons for pregnant smokers' low levels of attendance at supervised PA sessions should be investigated; findings could be used to increase attendance rates. For example, following on from recent work on barriers to PA,[115–117] further research is needed to explore barriers to attendance and to PA adherence during pregnancy, and to assess whether or not these barriers vary during different stages of pregnancy and among women with different comorbidities, including gestational diabetes and obesity.

3. Further methods of increasing PA adherence among pregnant smokers need to be developed and tested. For example, financial incentives have shown some benefit for aiding smoking cessation in this population and they may be used in combination with PA to increase both attendance at exercise sessions and smoking cessation.[12] In addition, interventions are needed that provide regular prompts to remind women to exercise (e.g. text messages or brief telephone calls); such interventions have been successfully piloted with young women but not yet with pregnant women.[118]
4. The reasons why few inactive pregnant smokers were attracted to a PA trial need to be identified and methods are needed to attract these less active pregnant smokers.
5. Studies are needed to establish whether or not the previously reported finding of a short bout of PA reducing cigarette cravings in pregnant smokers is a robust finding. So far, only one study has investigated this issue. If it is a robust finding, interventions need to be developed that can translate this benefit into prevention of smoking relapse.
6. There was no evidence of beneficial effects on maternal weight gain or depression. Studies are needed that focus on women who are at risk of higher maternal weight gain and on women who have high levels of depression at baseline.
7. Among pregnant smokers there was no evidence for a PA intervention having an added benefit for smoking cessation beyond that of usual care. However, it is possible that in some circumstances a PA programme alone may be more practical and may aid smoking cessation, and this needs to be assessed.
8. There were significantly fewer deliveries by caesarean section in the PA group than in the control group. Further studies are needed to replicate this finding and to explore the underlying mechanisms.

Implications for health care

There was no evidence that offering regular, supervised exercise and PA consultations, in addition to routine smoking cessation support, to women following their first antenatal visit is effective for aiding smoking cessation. Therefore, PA is not currently recommended for smoking cessation during pregnancy. One study showed that PA acutely reduces cigarette cravings in abstinent pregnant smokers[29] and, among smokers in general, PA is recommended for reducing these cravings.[21,22] In the present study there was no evidence for the PA intervention moderating cravings/urges to smoke, but it is possible that there are some acute benefits of PA on reducing cravings during pregnancy and the recommendation to use PA to manage cravings acutely remains for all smokers, including those who are pregnant. The PA intervention did not show any benefit for reducing maternal depression; in fact, there was a slight increase in depression in the PA group and therefore the intervention cannot be recommended for antenatal or postnatal depression in women attempting to quit smoking during pregnancy. There was no evidence for an effect of the intervention on maternal weight gain and therefore the intervention cannot be currently recommended for moderating this weight gain. There was no evidence of an increased level of AEs in the PA group and there was some evidence for a reduced incidence of caesarean sections in the PA group; therefore, in line with current guidance, PA remains indicated for general health benefits in pregnancy, including among pregnant smokers.

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Trial team

Chief investigator: Michael Ussher.

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Trial administrator: Mary Apps.

Trial Steering Committee: Jim Thornton (Chair), Ann McNeil, Tim Coleman, Michael Ussher, Sue Cooper, Kim Watts, Serena Cox (patient and public involvement/lay member).

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Contributions of authors

All authors made substantial contributions to the conception and design of the study and/or the acquisition of data and/or the analysis and interpretation of data, as listed below. All authors were involved in drafting the manuscript or revising it critically for important intellectual content. All authors approved the final version.

Michael Ussher (LEAP trial chief investigator/trial manager, Professor of Behavioural Medicine) was involved in the design, conduct, data acquisition, analysis and report-writing phases of the trial.

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Amanda Daley (Senior Lecturer in Behavioural Medicine) was involved in the design, analysis and report-writing phases of the trial specifically for the outcomes related to depression and maternal weight.

Holly Essex (Research Fellow in Health Economics) was involved in the design, analysis and report-writing phases of the trial specifically for the economic analysis.

Dale Esliger (Senior Lecturer in the Measurement of Physical Activity) was involved in the design, conduct, analysis and report-writing phases of the trial specifically for accelerometer data outcomes.

Tim Coleman (Professor of Primary Care) was involved in the design, conduct, analysis and report-writing phases of the trial.

Publications

Ussher M, Aveyard P, Manyonda I, Lewis S, West R, Lewis B, *et al.* Physical activity as an aid to smoking cessation during pregnancy (LEAP) trial: study protocol for a randomized controlled trial. *Trials* 2012;**13**:186.

Ussher M, Lewis S, Aveyard P, Manyonda M, West R, Lewis B, *et al.* Physical activity for smoking cessation in pregnancy: randomised controlled trial. *BMJ* 2015;**350**:h2145.

Data sharing statement

The guarantor (MU) is willing to examine all requests for the full data set after a period of 3 years from the date of this publication. Participants did not give consent for data sharing but the data are anonymised and the risk of identification is low.

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Appendix 1 Telephone screening sheet

Please add site ID no. ☐

To be completed by Researcher by phone:

Researcher's name:	
Date:	Time:
Potential participant's Name:	
Address: Email:…… Daytime tel:…….. Evening tel:…….. Mobile:…… Best time to call is between…… and…… Post Code: No. calls made:……	
GP's Name: Address: Tel:	
Introduction: Name/role, hospital, research study, spare a few minutes to discuss. **Describe study:** • Help with stop smoking. • Compare usual help/advice with usual help/advice plus exercise. • Around 900 women, several hospitals • Either once a week for six weeks or twice a week for six weeks then once a week for two weeks. 50:50 chance of either group. • Quit one week after first appointment. • Follow-ups at around 38 weeks pregnant, baby six months (at home if preferred) • Questionnaires and CO monitor • £7 travel expenses	

Eligibility Checklist:	**Inclusion criteria**	
1. How old are you?	Age 16 – 50	
2. How many weeks pregnant are you?	10-24 weeks	
3. How many cigarettes did you smoke on a typical day before you were pregnant?	≥ 5 cigs	
4. How many cigarettes do you smoke on a typical day now?	≥ 1 cigs	
5. Are you willing to try to stop smoking without using nicotine replacement therapy (e.g. patches)?	YES	
6. Can you read and write in English?	YES	
7. Are you available and willing to attend up to 14 appointments over the next 2 months?	YES	
8. Do you have a drug or alcohol problem?	NO	
9. Are you able to walk continuously for at least 15 minutes?	YES	
10. Have you been advised by a doctor, midwife or another health professional not to take exercise during your pregnancy?	YES	NO
11. Has a doctor ever said you have a heart condition and recommended only medically supervised physical activity?	YES	NO
12. Do you have chest pain brought on by physical activity?	YES	NO
13. Have you developed chest pain in the last month?	YES	NO
14. Do you tend to lose consciousness or fall over as a result of dizziness?	YES	NO
5. Do you have any bone or joint problems that become aggravated when you are more active?	YES	NO

16. Has a doctor ever recommended medication for your blood pressure or a heart condition?		YES	NO
17. Are you aware, through your own experience or a doctor's advice, of any other medical reason why you shouldn't be physically active without medical supervision?		YES	NO
18.If woman answers YES to any of Q10-17: Do I have your permission to contact a doctor at your hospital to check if it is ok for you to exercise? If woman answers no: She cannot take part.		YES	NO
If yes to Q10-17: Consultant has confirmed that it is safe for woman to take part?	NA	YES	NO
For all women who are eligible: Do I have your permission to contact your GP, midwife and obstetrician to let them know you are interested in taking part?		YES	NO
Sent letter to GP about participation?		YES	
Suitable for trial?		YES	NO
Information sheet & directions sent?		YES	

Date of first appointment:	Time: Clinic:

Remind the women to bring a pair of shoes comfortable for walking in, in case she is in the exercise group.

Appendix 2 Therapist manual for delivering behavioural support for smoking cessation

Smoking cessation support manual for LEAP trial

This manual includes guidance all 43 behaviour change techniques (BCTs), except BM4 "Provide rewards contingent on successfully stopping smoking", defined in the following taxonomy:
Michie S, Hyder N, Walia A, West R (2011) Development of a taxonomy of behaviour change techniques used in individual behavioural support for smoking cessation. Addictive Behaviour, 36, 315-9. The 43 BCTs used are:

Specific focus on the target behavior (*B*) and maximizing motivation (*M*): BM1. Provide information on consequences of smoking and smoking cessation; BM2. Boost motivation and self-efficacy; BM3. Provide feedback on current behavior; BM5. Provide normative information about others' behavior and experiences; BM6. Prompt commitment from the client there and then; BM7. Provide rewards contingent on effort or progress; BM8. Strengthen ex-smoker identity; BM9. Identify reasons for wanting and not wanting to stop smoking; BM10. Explain the importance of abrupt cessation; BM11. Measure CO. **Maximizing self-regulatory capacity and skill (*BS*)**: BS1. Facilitate barrier identification and problem solving; BS2. Facilitate relapse prevention and coping; BS3. Facilitate action planning/develop treatment plan; BS4. Facilitate goal setting; BS5. Prompt review of goals; BS6. Prompt self-recording, BS7. Advise on changing routine; BS8. Advise on environmental restructuring; BS9. Set graded tasks; BS10. Advise on conserving mental resources; BS11. Advise on avoiding social cues for smoking. **Promoting adjuvant activities (*A*)**: A1. Advise on stop-smoking medication; A2. Advise on/facilitate use of social support; A3. Adopt appropriate local procedures to enable clients to obtain free medication; A4. Ask about experiences of stop-smoking medication that the smoker is using; A5. Give options for additional and later support. **General aspects of interaction focusing on delivery of the intervention (*RD*)**: RD1. Tailor interactions appropriately; RD2. Emphasize choice; **General aspects of interaction focusing on information gathering** (RI): RI1 Assess current and past smoking behaviour; RI2. Assess current readiness and ability to quit; RI3. Assess past history of quit attempts; RI4. Assess withdrawal symptoms; General aspects of interaction focusing on general communication (RC): RC1. Build general rapport; RC2. Elicit and answer questions; RC3. Explain the purpose of CO monitoring; RC4. Explain expectations regarding treatment program; RC5. Offer/direct toward appropriate written materials; RC6. Provide information on withdrawal symptoms; RC7. Use reflective listening; RC8. Elicit client views; RC9. Summarize information/confirm client decisions; RC10. Provide reassurance.

The specific BCTs used are indicated in brackets in the manual below. The version of the manual used by therapists did not include these BCT labels.

Each smoking cessation consultation should take about 20 minutes.

Session 1: Preparation for quitting

Briefly describe the study and intervention and check volunteer's understanding:

- **Explain randomisation** e.g. 'A computer will decide whether you will get the standard treatment or the exercise programme. Do not be too concerned about which you are getting. Whatever you receive, you are in with a good chance of succeeding in stopping smoking. In both conditions we shall be providing help and support to help you to stay free of smoking.'
- **Remind them what the interventions will involve (RC4)** e.g. 'If you are in the exercise group you will need to attend 14 appointments over 8 weeks. This will involve waking on a treadmill for up to 30 mins and advice and support with stopping smoking and taking regular exercise. If you receive the standard treatment you will be asked to attend 6 weekly appointments providing advice and support with stopping smoking.
- **Explain the timing of the target quit date** (TQD): We will ask you to stop smoking one week from today. **(BS4)**
- The volunteer should not be randomised using the online database until you are satisfied that she understands what the study will entail (especially the need to attend all appointments) and understands the process of randomisation.

IF RANDOMIZED:

- **Explain the purpose of carbon monoxide (CO) monitoring (RC3)**
- **Measure CO (BM11) and use the reading to motivate quitting.**
  e.g. 'This shows how much you inhale the smoke and all the dangerous chemicals in it. A non-smoker would normally have a reading of less than eight. You as a smoker have a reading of ___. As soon as you stop smoking, this will start to go down to the non-smoking level. This will happen not just in your own body, but in the body of your baby as well. There is an immediate health benefit in stopping smoking. We shall repeat this measure once a week.'

- **Briefly discuss reasons for wanting to quit, level of motivation for quitting and confidence for quitting** (refer to questions in CRF) **(BM9, R12)**
- Assess and discuss current and past smoking behavior (see questions in CRF) (**RI1**)
- **Discuss past attempts at quitting (R13)** and reasons for relapse. Determine longest periods of abstinence and, if these are reasonably lengthy, use these as a reason to be optimistic to about being able to quit.
- **Discuss preparing for the quit day (BM6, BS3)**; e.g. "I suggest you make a list of the things you need to do to prepare for your quit day. For example: Tell people you are quitting, particularly those who will give you support **(A2)**, decide when you will have your last cigarette, tell people that they will not be allowed to smoke in the home, remove all ashtrays and from your home **(BS8)**, become aware of times when you are most likely to lapse (e.g. after meals, when alone in the house, on phone) and make a note of these **(BS6)**, think about how you will deal with these times and be aware that one puff can easily turn into a full relapse **(BS1)**." Also ask them to think about whether there are any events coming up that might make it difficult not to smoke (e.g., a stressful event or party, or meeting someone they used to smoke with) **(BS1)**. Mention that there will be more time to discuss these strategies on their quit day.
- **Discuss whether partner smokes** and whether partner or friends or colleagues might want to quit with them. Invite partner to join them at their treatment sessions. **(A2)**

- **If they have children**: discuss what they will do with children during the sessions. Also, suggest they explain to the children that they are quitting and that they ask the children to encourage them. **(A2)**
- Explain clearly that the woman can have the last cigarette before the session on their quit day (e.g. outside the clinic before coming in, on the morning or the night before their quit day. No smoking after that) **(BS4)**. If they can, ask them to decide now when they would like to have their last cigarette and say that it is their choice **(RD2).**
- **Give a leaflet about smoking and smoking cessation during pregnancy (BM1, RC5)**
- If they ask **whether they should start cutting down** in preparation for quitting, explain that it is better not to start missing cigarettes before the real quit attempt begins. This is likely to be a better way to quit than having long breaks between the last few cigarettes, enjoying them greatly, and saying 'goodbye ciggies' with tears in their eyes and having strong cravings before they have even quit.
- **If volunteer says they are content with cutting down to 2 or 3**, consider mentioning the following to encourage them to quit abruptly and completely **(BM10)**
- It is often anxiety and discomfort that motivates behaviour change rather than logic:

Encouraging Women to Quit Completely
Not much benefit to be had by cutting down as you inhale more deeply and more nicotine reaches the baby. You have the worst of both worlds as you are experiencing the discomfort of cutting down and doing the same harm to yourself and the baby.
You will be adding more stress making those few cigarettes more precious and there is also the stress of withdrawal between those few cigarettes. Better to quit completely.
It is best to quit completely now because the pressure that comes with having a new baby will make it more likely that you will relapse.

- If they ask about **self-rolled and low tar cigarettes** explain that these are just as harmful. **(BM1)**

Session 2: Quit Day

Objectives

- Remind patient that today is their quit day
  Look for reasons why woman is a good prospect (BM3) (e.g. managed to quit for a period of time in the past, she is highly motivated, lessons learned from previous attempts, success/change in other areas of their life, is receiving best available support etc.). Express your optimism. Make it clear that they need to be prepared for it being very difficult (particularly if quitting was difficult in the past, CO is high and/or they smoke their first cigarette soon after waking), but that many women in their position quit successfully

- **Stress the importance of a good start**. e.g. 'You have shown determination by getting as far as this. Now is the crunch time. Even if the first few days prove to be difficult, do not go back to smoking. As a long-term smoker, you need to expect at least some difficult moments. The good news is that there is strong evidence that making it through the first week without a single puff massively increases your chances of success. Please remember this when you are tempted to smoke.
- **Explain the withdrawal symptoms** that they may experience. 'Besides cravings, many people feel irritable, depressed, restless, have poor concentration, sleep disturbance and feel hungrier.' Also some people get more colds, mouth ulcers and headaches. **(RC6).** Reassure that these will gradually decrease across the first 3-4 weeks of quitting. The first week often is the hardest and the middle of the first week is often the worst time.
- **Smoking and stress:** Explain that smoke increases rather than reduces stress and that most people feel less stress within a week or two of quitting.
- **If they are ambivalent about quitting** remind them of why they want to quit.
- **Discuss possible obstacles to success and briefly review coping strategies** for week ahead: Ask 'What happened when you tried to stop smoking before? Refer woman to tips in the leaflets. Ask "Are there any particular events this week that might increase your temptation to smoke?" **(BS1)**

  Explain that cravings often only last a few minutes and that they tend to peak and then subside. Recommend that they prepare for these cravings **(RC6)** (e.g. distract yourself, have an activity ready, for exercise group suggest a short walk, have someone you can call when you are close to lapsing, keep healthy snacks in your bag (e.g. apples, carrot sticks) and water (some people say that sipping helps with cravings), have things to keep your hands occupied, avoid/minimize difficult/stressful/tempting situations if you can (e.g. parties, time spent with smokers,), especially in the first few weeks **(BS11)**. If they cannot avoid these situations suggest they be prepared for it to be a challenge. Explain that it can also be useful to change their daily routine (e.g. if they usually smoke first thing in the morning suggest they replace this with something else, such as a shower or breakfast). **(BS7)** Suggest that they also conserve their energy, particularly in the first few weeks, by not taking on major new projects such as making other significant changes in their life **(BS10)**.

- A typical tempting situation which may lead to smoking is when people are bored with not much to do. If this affects you, make plans for distracting yourself. To give you an example, Mrs. Palmer found that for her, making a jigsaw helped. She started a jig-saw puzzle on her quit day and when tempted to smoke went and looked for the next piece of her jigsaw.

- **Suggest cognitive strategies (RC6)** . Some people benefit from 'talking themselves through' difficult situations; e.g. remind yourself that the difficult moment will soon pass, remember your reasons for stopping smoking and the danger of having even one slip, think of all you've achieved so far, think how you will feel if you lapse and have a cigarette, write down all the reasons why you don't want to smoke and keep this with you, keep a picture of the baby's scan with you.
  - 'If tempted to smoke, have a look at the tips in this leaflet. Distract yourself if it gets tough. Take it one day or even one hour at a time. **(BS9)**

  Remember that if you pull through this week without smoking at all, you are far more likely to succeed.

- If they make these preparations this will **build up their resistance** when they are tempted to smoke.
- **Finish by stressing the importance of not having a single puff of a cigarette** as this can quickly lead to having more cigarettes and it will increase your cravings. You may feel that having just one cigarette won't hurt and will make you feel better. Be on your guard! This is how attempts at quitting fail. Do not fool yourself. **(BS2)**

Session three : one week after quit day

Main aims :

- **Assess CO** and give feedback about whether their reading has reduced **(BM11, BM3).**
- **How do I handle discrepancies between CO and self-report?**
  - Best not to challenge self-reports, but check again that client did not smoke
  - Check ambient CO
  - Check your own reading
  - Ask about the possibility of exposure to secondary tobacco smoke.
  - Ask about possibility of exposure to CO at home (e.g. leaky gas boiler)
  - Say that you will calibrate the CO monitor and check their reading again again next week
- **Review** how they got on this week with remaining abstinent and discuss whether the strategies they prepared were helpful. **(BS5)**
- **Boost motivation**, provide orientation on withdrawal, discuss possible reasons for relapse and strategies for dealing with these **(BS2)**.
- **Reinforce abstinence**, deal with lapses.

Check smoking status. If abstinent, praise and reinforce: e.g. **"**If you did not smoke at all, you are now free of nicotine and of many other chemicals in cigarette smoke which are bad news for your baby" (**BM7**).

- **If they lapsed,** explain again the importance of complete cessation, but do not discourage (e.g. 'You still have time to catch up. How do you plan to go about it?'*).* Discuss a plan. Look for a positive angle. Explain to lapsers who complain of withdrawal discomfort that this will only go away if they do not smoke at all – see below. Check for unrealistic expectations ('e.g. Despite the exercise/NRT, I still fancied a cigarette'). **If they have relapsed** back to regular smoking encourage them to learn from why they relapsed and to set a new quit date **(BM6)**. If they have relapsed, discuss whether they would consider using NRT **(RD2)** and provide **advice about NRT (A1)**. Liaise with the PCT to enable them to get free NRT **(A3)**.

- **Discuss withdrawal discomfort** and refer to their responses to the withdrawal questions in the CRF **(R14)**. Reassure where appropriate *(*e.g., 'Over many years, your brain and body have got used to having regular shots of nicotine throughout your waking hours. Once you stop smoking, it can take weeks and months to regain your balance.'*)*. Explain the likely duration of concrete symptoms patients are concerned about. Reassure them that most smokers experience strong withdrawal symptoms and that cravings are the most common symptom **(BM5, RC10)**; e.g. "They can be unpleasant, but they will not harm you. You will be over the most difficult time soon". Suggest they continue to be aware of, or make a note of, when they are most tempted to smoke **(BS6)**.
- **Discuss triggers for relapse and coping efforts (BS2)** where appropriate. Encourage them to use: distraction techniques (I go and do something, get away from the situation, etc.), avoiding temptations (I do not have any cigarettes in the house, did not go to the pub this week), and cognitive approaches (I think of my reasons for stopping, tell myself to take one day at a time, I imagine how bad/guilty I will feel if I smoke etc.).
- Suggest they start **seeing themselves as a non-smoker**, rather than as a smoker who is trying to quit or an ex-smoker. If they do this they are more likely to succeed. (e.g. if someone offers them a cigarette suggest they say 'No thanks, I don't smoke', and ask them to imagine saying this) **(BM8)**.
- Allow time at the end of each session for the **participant to ask questions (RC2)**.
- Remind participant that if they attend all six smoking cessation sessions they will be entered into a **prize draw** for three £100 shopping vouchers. **(BM7)**

Sessions 4 (two weeks after quitting) onwards

Main aims:

Reinforce abstinence or deal with lapses.

Give reassurance on withdrawal (at later sessions deal with weight gain).

Discuss obstacles, advise on coping, express support.

Tailor the content for each individual **(RD1)**

- **Check smoking status (BS5).** Congratulate abstainers and praise them. Explore how they got through difficult moments; elicit, reinforce, and develop coping strategies. Note they are now making it (first 2 weeks) or have made it through the most difficult part of quitting.
  If not abstinent, discuss barriers to quitting. Explain the urgency of catching up
- **If a participant is smoking** daily, debrief on difficulties that led to smoking, and suggest lessons learned and future solutions (**BS2**). Help patient decide whether to continue current quit effort or to set a new quit date (**BM6**). Frame the experience positively, and focus on future efforts. Offer to refer them to the PCT for further support during or following the research intervention **(A5)**.
- **Discuss triggers for relapse and coping strategies (BS2)**
- **If you go through a difficult patch**, remember that it will get easier soon. Your brain and body got used to regular doses of nicotine. It can take a few weeks, or more, to get back your balance and to learn to live without smoking. Most people feel OK within some three or four weeks.

- **Ask about use of NRT**: refer to the questions in the CRF and, for those who are using NRT, ask how they are getting on with it. **(A4)**
- **Emphasise the rationale of recommending complete abstinence** and the danger of relapse.
- By now, you have probably **saved quite a bit of money** you would otherwise spend on cigarettes. This saving will grow quickly. Plan how to spend it on yourself.

FU at six weeks after quitting: remember that you **need to conduct a 7 day physical activity recall via telephone for control group 6 weeks after quit.**

- Explain the danger of relapse and the need to stay on guard. 'Many smokers who make it through pregnancy go back to smoking after the birth or within a year of quitting. I would like to make sure that this will not happen to you'. (**BS2**)
- Warn against 'transgression' cigarettes when stressed, when bored, on holidays, and in company. Discuss the temptation people often have 'to try one cigarette, just to see', explain the dangers, especially in the hours and days after the birth. **(BM8, BS2)**
- Discuss likely relapse situations (e.g. smokers they will come in contact with soon after the birth) and plan coping strategies. (**BS2**)
- Emphasise woman's ability to cope and implement cessation procedures on their own, building on the success to date.
- The woman may be concerned about what will happen after the visits finish. In case they need to contact you, give them your clinic phone number. Offer them the option of being referred on to the PCT stop smoking service for further support. Give them information about the NHS website for pregnant smokers (www.smokefree.nhs.uk/smoking-and-pregnancy/) **(RC5)** and the smokefree helpline: 0800 022 4332. **(A5)**
- If they say they feel tempted in the company of smoking friends/family, suggest they consider asking these individuals not to smoke around them, or just plan how to react when one of them lights up or offers a cigarette. (**BS2**)
- "One of these days you will realise that you have not thought of smoking at all for hours. Notice this. It will soon become days and then weeks, until cigarettes will stop being an issue at all."
- "Every day you make it without smoking, you are learning how to cope without cigarettes and finding your own ways to overcome difficult moments. Notice what helps and use it."
- "The link between smoking and everyday activities such as getting up in the morning, speaking on the phone, or having a meal will by now be weakening – notice such positive developments."
- "If you still have difficult moments, do not fall into the trap of thinking that one cigarette will not hurt. Even a puff could put you in serious danger of undermining all you have achieved so far." (**BS2, BM8**)
- "Try to eat a healthy, balanced diet. This includes plenty of fruit and vegetables, and not too much fried and fatty food. Keep a supply of healthy snacks with you. Watch out for high calorie, high fat snacks, but do not go hungry."

Tips for preventing relapse (BS2)

If you have not smoked at all, or very little, for over four weeks now, you are really getting there. Once the regular support is over, here are some tips to prevent you going back to smoking:

- Think ahead of situations which could be dangerous for you. Boredom? Stress? Getting drunk? Wanting to enjoy yourself? Think now how you are going to cope. When the situation comes, remember how you prepared for it.
- Do not think that after being a non-smoker for a few months, one cigarette will not make any difference. It will be as dangerous as ever.
- Even if things are still difficult on occasions, sooner or later, you will lose interest in smoking, or even start to dislike the very idea of it. You are very close now to join millions of others who have stopped smoking for good.

Some women who quit smoking successfully when pregnant start to smoke again after they give birth. Stay on your guard.

- Passive smoking is harmful for your baby.
- Quitting smoking is very difficult. You have now done the hard part. It would be a shame to spoil it all.
- Sooner or later you will start thinking of yourself as a non-smoker and the idea of smoking will start to look rather strange and less appealing.

Notes on the support process (this also applies to physical activity counselling)

Key things to remember:

- **Summarise** information the women needs to remember **(RC9)**.
- **Reflective listening**: reflecting back to the women what they are saying, particularly the emotional content (e.g. I can appreciate that it makes you angry and frustrated to see your partner continuing to smoke around the house when you have quit). **(RC7)**
- **Acknowledge their fantasies** about smoking, but explain why they are unrealistic (e.g. Yes, I can see that you would love to have the occasional cigarette, but smokers who do this very quickly start smoking on a daily basis back to their original levels of smoking). In general, try and explore their views on smoking cessation (**RC8**).
- **Descriptive praise**: describe what they are specifically doing well at and praising them for this (e.g. you did well to throw all your cigarettes away because I know you partly wanted to keep some for an emergency), rather than just using general praise (e.g. you are doing very well). **(BM4)**
- **Preparing for success**: Focus on helping the women to plan so that things go right (e.g. preparing for triggers to smoking), rather than having to 'react' when things go wrong **(BS1)**.
- **Maintaining a positive tone** e.g. avoid criticism, use pleasant tone of voice and body language, focus on solutions rather than problems, keep your sense of humour! **(RC1)**

For those familiar with psychological counselling, it is important to note that brief smoking cessation support is much more directive and goal-oriented than general counselling approaches.

Appendix 3 Therapist manual for delivering the physical activity intervention

Physical Activity Intervention Manual
(refer also to participant's handbook)

This manual includes guidance on 19 of 40 behaviour change techniques (BCTs) defined in the following taxonomy: Michie S, Ashford S, Sniehotta FF, Dombrowski SU, Bishop A, French DP (2011) A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: the CALO-RE taxonomy. Psychological Health, 2, 1479-98.
The 19 BCTs covered in this manual are: 1. Provide information on consequences of behaviour in general; 2. Provide information on consequences of behaviour to the individual; 7. Action planning; 8. Barrier identification/problem solving; 9. Set graded tasks; 10. Prompt review of behavioural goals; 12. Prompt rewards contingent on effort or progress towards behaviour; 13. Provide rewards contingent on successful behaviour; 16. Prompt self-monitoring of behaviour; 20. Provide information on where and when to perform the behaviour; 21. Provide instruction on how to perform the behaviour, 22. Model/Demonstrate the behaviour; 23. Teach to use prompts/cues; 26. Prompt practice; 27. Use of follow-up prompts; 29. Plan social support/social change; 34. Prompt use of imagery; 35. Relapse prevention/coping planning; 38. Time management.

The specific BCTs used are indicated in brackets in the manual below. The version of the manual used by therapists did not include these BCT labels.

Each consultation should take about 20 minutes.

Session 1 (one week before quit date)

- **Review her current PA levels** (refer to seven day recall of physical activity).
- **Explain how to use treadmill (BCT 21:** Instruction on how to perform behaviour**)**

- Explain warm-up (3mins walking, hold stretches for 10 secs for front thighs, calves, hamstrings and reach overhead for upper body) and warm down (slow down for final minute of walking, repeat stretches)
- Recommend rating of perceived exertion of 12-14 and show RPE chart. Explain about 'Talk Test', and that exercise should be intense enough for her to be breathing heavier than normal
- Demonstrate use of treadmill (**BCT 22**: Demonstrate behaviour)
- Ask women to walk on treadmill for 15-30 mins
- Agree how long she will walk (it is fine if she exceeds this goal, as long as it is no more than 30 mins)

- **Discuss benefits of exercise (BCT 1:** Provide information on consequences of behaviour in general**)**

- Mention that regular exercise has been shown to reduce cravings in a similar way to nicotine replacement.
- Mention that exercise is also good for a healthy pregnancy. Say that there will be more time to discuss these benefits at the next session.

● **Agree PA goals for this week (BCT 7:** Action planning**)** for exercise she will do outside the treadmill Sessions:
- Recommend she starts with at least one session of 15 mins PA.
- Recommend that she gradually progresses towards 30 mins of PA on 3 to 5 days a week (plus treadmill sessions).
- Agree a SMART goal, e.g. 'I will walk for 20 mins around the park at lunchtime, on 5 days this week'.

● **Explain how to use pedometer**
- Ask her to wear pedometer for the rest of today and to take it off last thing at night and then to open it and record the number of steps in the diary.
- Each morning, ask her to put pedometer on as soon as she gets up and to wear it all day. Again, taking it off last thing at night and recording the number of steps (**BCT 26**: Prompt practice). Say that she can keep the pedometer.

● **Ask her to complete PA and steps diary** for everyday this week (**BCT 16**: Self-monitoring of behaviour). Write her PA goal for this week on the top of the diary.

Session 2 (few days before quit day)

● **Review goals/plans**
- Check whether she has managed to do any PA in her own time since the last session
- Briefly review woman's goals for taking PA in her own time for week ahead (**BCT 10:** review of behavioural)
- Check she has been able to use the pedometer OK and is recording her daily steps. If she is averaging less than 10,000 steps a day recommend a 10% increase in her current steps over the next two weeks (**BCT 7:** action planning, **BCT 9:** set graded tasks).

● **Go though physical activity booklet with woman**
- Ask her to write down what she sees as the main benefits and disadvantages (if any) of becoming more active during her pregnancy and remind her of other benefits (**BCT 2**: Consequences of behaviour to the individual).
- Testing times: ask her to write down any barriers that might prevent her from achieving her PA goal and think of ways of overcoming these barriers (**BCT 8:** Barrier identification problem solving).
- Go though the tips for exercising in the booklet and praise her for any specific adjustments she has made to her lifestyle to encourage exercise (**BCT 12**: Rewards contingent on effort or behaviour). Suggest that she rewards herself when she achieves her exercise goals (e.g. a special meal at the end of the week) (**BCT 13**: Reward contingent on successful behaviour).
- Demonstrate the home exercises in the booklet and ask her to try each of the level 1 exercises/stretches with you. **(BCT 21:** Instruction on how to perform behaviour, **BCT 22**: Demonstrate behaviour). Encourage her to practice the exercises at least once before the next meeting (**BCT 26**: prompt practice). When she is confident with the level 1 exercise, go through the Level 2 exercises/stretches at a future session.
- Provide information on local opportunities for exercise (e.g. walking schemes, antenatal exercise classes) (**BCT 20:** information on where and when to exercise).
- Encourage her to exercise at regular times (e.g. a walk after lunch) so that it becomes a habit (**BCT 23:** Teach to use prompts/cues). If she has raised lack of time as a barrier to exercise, suggest she manages her time to fit in exercise by timetabling exercise slots into her week (**BCT 38**: time management).
- Suggest she tries to find people who will exercise/walk with her (**BCT 29**: Plan social support).

● **Ask woman to walk on treadmill for 15-30 mins**
- If she walked for less than 30 mins at the last session recommend that she walks for 5 mins longer this time and at each further session, until she is walking continuously for 30 mins.
- Agree how long she will walk for.
- After exercise: Remind woman to complete PA and steps diary every day this week.

Session 3 (quit day)

● Briefly review physical activity the women has done in her own time and adjust goals for physical activity in general and for pedometer (**BCT 10:** review of behavioural goals)
● Discuss any barriers that might prevent her from achieving her PA goal and think of ways of overcoming these barriers (**BCT 8:** Barrier identification problem solving).
- Praise her for any specific adjustments she has made to her lifestyle to encourage exercise (**BCT 12**: Rewards contingent on effort or behaviour). Discuss how she is rewarding herself when she achieves her exercise goals (**BCT 13**: Reward contingent on successful behaviour).

● Set heart-rate zone and ask woman to wear HR monitor while on treadmill:
HEART RATE TARGETS/(training zone):

Less active (ie reporting less than 150 mins PA in the last week), overweight (BMI=25 – 29.9) or obese (BMI=30+) women:
Start with light intensity heart-rate range:
Aged 16-29: 102 -124 bpm
30 years plus: 101-120 bpm

Gradually progress to moderate intensity HR range:
Aged 16 -29: 125 -144 bpm
30 years plus: 121-144 bpm

Active women (ie reporting at least 150 mins/week):
Moderate intensity HR range:
Aged 16-29 145-160 bpm
Aged 30 plus 140-156 bpm

● Ask woman to walk on treadmill for 15-30 mins
● Ask woman to check that she keeps her heart rate in the training zone, and ask her to maintain her walking at a level where she is still able to hold a conversation
● Give exercise diary and ask her to fill it in each day this week.

Consultation Session 4 (one week after quit day) onwards

● Review physical activity the women has done in her own time:
- Discuss barriers that may prevent her maintaining and increasing her physical activity and how she might deal with these (**BCT 35**: relapse prevention/planning)
- Agree plans for PA for the coming week:
- Refer back to physical activity booklet if necessary
● Praise her for any specific adjustments she has made to her lifestyle to encourage exercise (**BCT 12**: Rewards contingent on effort or behaviour). Discuss how she is rewarding herself when she achieves her exercise goals (**BCT 13**: Reward contingent on successful behaviour).
● Review whether she has found people who will exercise/walk with her.

- Review exercises in booklet.
- Ask woman to walk on treadmill for 15-30 mins
- Ask her to imagine herself becoming fitter and healthier and to imagine herself walking briskly with energy and with lungs free of tobacco (**BCT 34**: use of imagery)
- Remind her that for the last two weeks of the exercise programme you will see her once a week rather than twice a week (**BCT 27**: use of follow-up prompts).

Notes on the support process

Key things to remember:

- **Summarise** information the women needs to remember
- **Reflective listening**: reflecting back to the women what they are saying, particularly the emotional content (e.g. I can appreciate that it is very difficult to find the time to exercise).
- **Descriptive praise**: describe what they are specifically doing well at and praising them for this (e.g. you did well to buy some new trainers; this shows that you are serious about taking more physical activity), rather than just using general praise (e.g. you are doing very well).
- **Preparing for success**: Focus on helping the women to plan so that things go right (e.g. preparing for when it rains), rather than having to 'react'.
- **Maintaining a positive tone** e.g. avoid criticism, use pleasant tone of voice and body language, focus on solutions rather than problems, keep your sense of humour!

Appendix 4 Participant physical activity booklet

LEAP

Name:.....

Guide to physical activity during your pregnancy

BENEFITS

Regular physical activity during your pregnancy has many benefits for you and your baby; such as:

- Less varicose veins, leg cramps and swelling of the legs
- Better posture, balance and muscle tone
- Reduced constipation and back ache
- Easier and shorter labour, in many women
- Better mood, sleep and energy
- Less tobacco withdrawal symptoms (such as feeling irritable) and cravings, and an increased chance of becoming a non-smoker

Write down what you feel are the main benefits and disadvantages for you of becoming more active during your pregnancy:

BENEFITS	DISADVANTAGES

- Can you think of any way of overcoming the disadvantages?

- If you think of any more benefits add them to the list.

Set a realistic goal each week for how much activity you can manage each day

MY GOAL:

- Aim to gradually build up to 30 minutes of activity each day.

TESTING TIMES

- Write down anything that might stop you from achieving this goal
- Try and think of what you can do when this happens

Why I might miss a day's exercise	What I can do when this happens

SOME TIPS

1. Don't smoke, walk!
When you feel a strong craving for a cigarette try going for a brisk walk, even if it is only for 5 minutes. Soon you will start feeling like a non-smoker.

2. Make it Fun
• Choose activities which you enjoy, and which fit easily into your day. Try walking part of the way to or from work or the shops. How about swimming
or following your home exercise routine?
• Play music while you're exercising.
• Involve friends or family.

3. Do it every day
• Gradually increase the number of days on which you are active.
• Then increase the time you are active for each day.
• Gradually build up to 30 minutes of physical activity each day.

4. Make it a habit
• Exercise at the same times each day, so that it becomes a habit.
• Try starting the day with a few gentle exercises or going for a walk.

5. Take it easy
• Choose activities that make you breathe slightly harder than normal, but are not hard enough to stop you having a conversation.
• Do just a little more (10-20 minutes extra) each week.
• Give your body time to adjust to being pregnant and to being without cigarettes.

6. Reward yourself
• Each extra day that you are a non-smoker and have reached your exercise goal give yourself a treat.
• Give yourself an extra treat at the end of each week; something like a special meal.

7. Plan ahead
Plan ahead for interruptions such as bad weather - an ideal opportunity to try your home exercise routine!

8. Keep a diary
Keep a daily record of how many minutes exercise you do and how many steps you do. It will help you to see your progress.

LOOK AFTER YOURSELF!

1. When to avoid exercise

- If you feel unwell, extremely tired or have just eaten a meal.
- In very hot or very humid conditions.

2. When to stop exercising

Stop exercising immediately if you feel any dizziness, nausea, severe pain or tiredness, extreme breathlessness or cold sweats.

3. Breathe Freely

- Keep breathing freely whilst you are exercising.
- To ease breathing: stop and lift your arms up and out.

4. Drink plenty of water Before, during and after exercise.

5. Have a healthy snack soon after exercising, such as a banana.

6. Avoid exercising on your back.

- During the middle and later stages of your pregnancy exercising on your back can cause discomfort.
- It may also reduce your blood pressure for a short time.

7. Pace yourself

Start slowly and gradually work up to a pace where you are breathing slightly heavier than normal, but not gasping for breath.

HOME EXERCISE PROGRAMME

1. **Build up gradually**
   - For each exercise aim for a number of repetitions which you can handle comfortably
   - Aim to gradually build up the number of repetitions you do, until you can do 20 or more
   - If you want to exercise for longer you can gradually build up to two or more complete circuits of all the exercises

2. **Taking breaks**
   - At first you may made need a short break between exercises
   - Gradually reduce the length of the breaks, so that eventually you do the exercises continuously

3. **To avoid aggravation or injury:**
   - Start slowly. Give your body time to warm-up
   - Avoid locking your knees when you are standing
   - Keep good posture, with a straight back.
   - Finish by doing some stretches.

4. **Moving up a level**
   Start with the exercises at level 1. When you are comfortable with level 1 move on to level 2.

If you exercise at home, as opposed to in a class, you can choose when, how and at what pace you exercise! Alternatively, you may prefer to exercise in a class, in which case you should inform the teacher that you are pregnant.

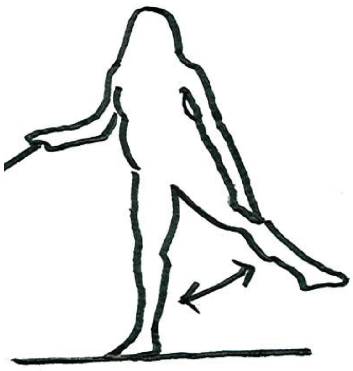
LEVEL 1 EXERCISES

- Try starting with 5 repetitions of each exercise. Over several weeks,
  gradually build to 20 repetitions

- Do at least 10 minutes of exercise by going through all the exercises several times

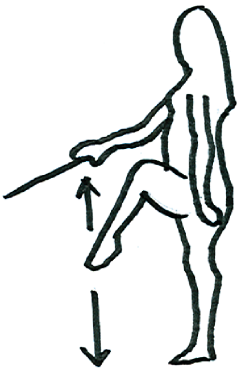
1. Side arm raise

2. Raise on toes

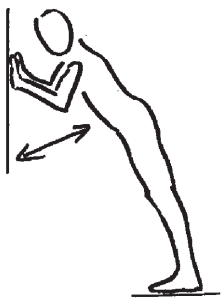


3. Side leg raise

4. Front arm raise



5. Knee raise

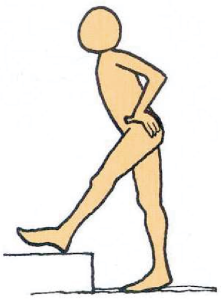


6. Wall-push up

LEVEL 1 STRETCHES

- Stretch regularly to help you feel loose and relaxed. Stretching also will help you with your posture and balance during pregnancy
- Stretch when you are warm, after you have done your other exercises
- Hold the stretch so that you feel a pleasant stretch, do not force the stretch. Avoid any bouncing movements.

1. Pull heel to buttock.
(for front of thigh)



2. Lean over straight leg
(for back of thigh)

3. Reach arms overhead.
(for arms and sides of body)

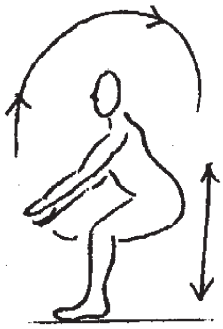
4. Lean on wall, straighten back leg.
(for calves)

Hold each stretch for 10 seconds

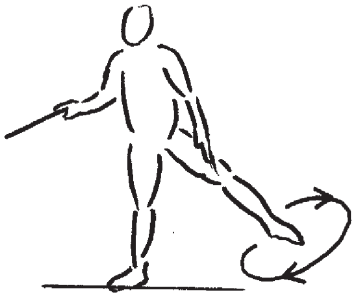
LEVEL 2 EXERCISES

Here are some slightly harder exercises for you to gradually build in

1. Side arm raise + toe raise



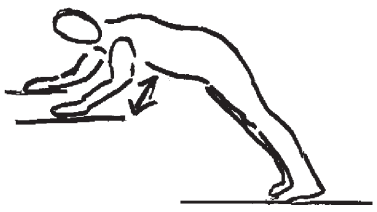
2. Backwards arm circle + leg bend



3. Leg circle

4. Front arm raise + knee raise

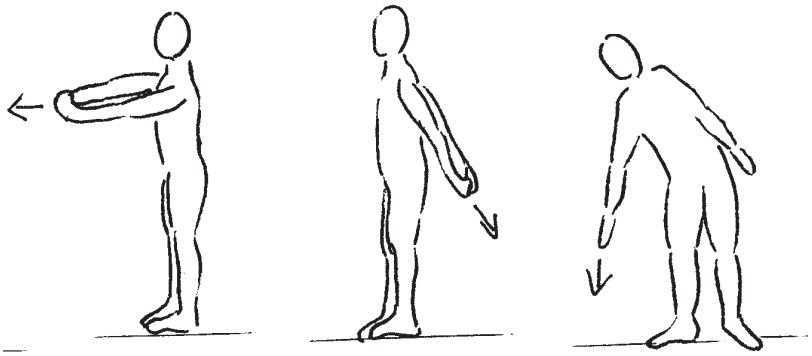
5. Overhead-arm reach + leg bend



6. Push-up on chair

LEVEL 2 STRETCHES

Here are some extra stretches



1. Pull arms forward (upper back & shoulders)

2. Pull arms back (chest & shoulders)

3. Bend to side (waist)

5. Press down on inner thighs (inner thighs)

Hold each stretch for 10 seconds

Appendix 5 Physical activity questionnaire

Instructions for carrying out the 7-day physical activity recall interview

1. *Label* the days on the recall table (day 1 is yesterday).
2. *Introduce interview*: Explain that you will be asking about their physical activity, starting with yesterday and working backwards through the previous 7 days.
3. *Define segments of the day*: Say that you will be asking separately about activities for the morning, afternoon and evening.
4. *Describe the type of activity* that you are interested in: Explain that you are interested in any work, household or leisure activities lasting at least 10 minutes that are at least at a level of intensity that makes them breathe slightly harder than normal, makes them warmer and makes them aware that their heart is beating faster. Say that you are *not interested* in light activities such as desk work, strolling or light housework.
5. *Ask about activities*: For each segment of the day, ask the woman to recall activity episodes lasting at least 10 minutes and record the information in the table (round to the nearest 5 minutes). For each activity record the type of activity (using type codes) and duration of activity in minutes (e.g. 'W 10' denotes a 10-minute walk). For each day begin by asking 'What did you do and where did you go on that morning'.
6. Record the number of minutes of activity for each day and the total minutes for the week. Enter the latter figure into the database.

TABLE 22 Seven-day recall of physical activity

Day	Morning	Afternoon	Evening	Daily minutes of activity
1 (yesterday)				
2				
3				
4				
5				
6				
7				
Weekly total:				

Cyc, cycling; D, dancing; DIY, do it yourself; Exf, structured exercise facility; Exh, structured home exercise; G, gardening; H, housework; Occ, occupational; Spi, sport/individual; Spt, sport team; Sw, swimming; W, walk; O, other (please state).

Appendix 6 Questionnaires

All questionnaires were presented on an online server.

Baseline questionnaire

Participant enrolment details

ID No:

Briefly describe the study and intervention and check volunteer's understanding:	
If they are still willing to participate ask them to sign the consent form and request a randomisation code:	

Participant's date of birth:	
Participant's initials:	
Ethnicity **(see below)**	
NHS number:	
Hospital no:	
Expected date of delivery:	/ /
Midwife's name:	
Midwife's telephone numbers:	Work Mobile
Name and role of person giving intervention at enrolment:	
If research midwife, are you case loading the participant?	Yes/no
Please enter the visit date:	/ /

How would you describe your ethnic group? (*Please check one box only*)	**White**		**Mixed**	**Asian or Asian British**	
	British	1☐	White & Black Caribbean 4☐	Indian	8☐
	Irish	2☐	White and Black African		
	Other	3☐	White & Asian		
			Other Mixed		

	Black or Black British	**Chinese or Other Ethnic Group**
	Black Caribbean 12☐	
	Black African 13☐	
	Other Black 14☐	
Before you became pregnant how many cigarettes did you usually smoke each day?	☐	
How many cigarettes do you usually smoke each day now?	☐	
Did you smoke in a previous pregnancy?	Yes ☐1 No ☐0 Not applicable ☐2	
How soon after you wake up do you smoke your first cigarette?	Within 5 minutes ☐ 3 6-30 minutes ☐ 2 31-60 minutes ☐ 1 After 60 minutes ☐ 0	
Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes ☐ 1 No ☐ 0	
Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes ☐ 1 No ☐ 0	
Which cigarette would you hate to give up the most?	The first one in the morning ☐ 1 Any other ☐ 0	
Do you smoke even if you are so ill that you are in bed most of the day?	Yes ☐ 1 No ☐ 0	
If you have a partner, does your partner smoke tobacco?	Yes ☐1 No ☐0 Not applicable ☐2	

Confidence for quitting

How high would you rate your chances of giving up smoking, at least until your baby is born?					
Very low	Low	Not very high	Quite high	Very high	Extremely high
1	2	3	4	5	6

Withdrawal symptoms questionnaire

Please show for each of the items below how you have been feeling over the past week.					
	Not at all	Slightly	Somewhat	Very	Extremely
Restless	1	2	3	4	5
Irritable	1	2	3	4	5
Depressed	1	2	3	4	5
Hungry	1	2	3	4	5
Poor concentration	1	2	3	4	5
Poor sleep at night	1	2	3	4	5
Anxious	1	2	3	4	5

Urges to smoke

How much of the time have you felt the urge to smoke in the past week?					
All the time	Almost all the time	A lot of the time	Some of the time	A little of the time	Not at all
5	4	3	2	1	0

How strong have the urges been?					
Extremely strong	Very strong	Strong	Moderate	Slight	No urges
5	4	3	2	1	0

Pregnancy history and demographics

How old are you?	☐ years
How many weeks pregnant are you?	☐ weeks
How many previous pregnancies have you had that have gone beyond 24 weeks?	☐
How many births have you had that were between 24 and 37 weeks of pregnancy?	☐

How many children are in your household?	
Of these how many are you the biological mother of?	
Are you the biological mother of children in any other household?	Yes ☐ 1 No ☐ 0
If yes, how many?	
Are you….	Married or Living with a partner ☐1 Single/divorced/separated/widowed ☐0
How old were you when you left full time education?	or tick ☐ if still in FT education
What is your usual occupation?	☐ No usual occupation

Use of Alcohol

How often do you currently have a drink containing alcohol?				
Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week

How many drinks containing alcohol do you have on a typical day when you are drinking? *(a drink is equivalent to a glass of wine, 1 spirit, or half pint beer)*				
1 or 2	3 or 4	5 or 6	7 to 9	10 or more

Feelings questionnaire (EPDS)

We would like to know how you are feeling. Please check the box that comes closest to how you have felt IN THE PAST 7 DAYS, not just how you are feeling today.
1. I have been able to laugh and see the funny side of things. 0☐As much as I always could 1☐Not quite so much now 2☐Definitely not 3☐Not at all
2. I have looked forward with enjoyment to things. 0☐As much as I ever did 1☐Rather less than I used to 2☐Definitely less than I used to 3☐Hardly at all
3. I have blamed myself unnecessarily when things went wrong. 3☐Yes, most of the time 2☐Yes, some of the time 1☐Not very often 0☐No, never
4. I have been anxious or worried for no good reason. 0☐No, not at all 1☐Hardly ever 2☐Yes, sometimes 3☐Yes, very often
5. I have felt scared or panicky for no very good reason. 3☐Yes, quite a lot 2☐Yes, sometimes 1☐No, not much 0☐No, not at all
6. Things have been getting on top of me. 3☐Yes, most of the time I haven't been able to cope at all 2☐Yes, sometimes I haven't been coping as well as usual 1☐No, most of the time I have coped quite well

0 ☐ No, I have been coping as well as ever
7. I have been so unhappy that I have had difficulty sleeping. 3 ☐ Yes, most of the time 2 ☐ Yes, sometimes 1 ☐ Not very often 0 ☐ No, not at all
8. I have felt sad or miserable. 3 ☐ Yes, most of the time 2 ☐ Yes, quite often 1 ☐ Not very often 0 ☐ No, not at all
9. I have been so unhappy that I have been crying. 3 ☐ Yes, most of the time 2 ☐ Yes, quite often 1 ☐ Only occasionally 0 ☐ No, never
10. The thought of harming myself has occurred to me 3 ☐ Yes, quite often 2 ☐ Sometimes 1 ☐ Hardly ever 0 ☐ Never

Physical activity, height, weight and CO reading

How confident are you that you will be able to do thirty minutes of physical activity (e.g. take a regular walk) on at least 5 days of the week during your pregnancy?

Not at all confident	Slightly confident	Moderately confident	Very confident	Extremely confident
1	2	3	4	5

What effect do you think being physically active (e.g. a brisk walk) will have on your success at quitting?

Large negative effect	Moderate negative effect	Slight negative effect	No effect	Slight positive effect	Moderate positive effect	Large positive effect
-3	-2	-1	0	+1	+2	+3

Maternal height (cm)	
Maternal weight (kg) as measured at booking appointment	or tick ☐ if unknown
Maternal weight (kg) as measured at this visit	

Exhaled Carbon Monoxide (CO) reading	ppm

Have you conducted an interview of seven day recall of physical activity?	☐ tick
Record total number of minutes of physical activity in the previous week	minutes

Record the main type of physical activity (*check one box only*):

- ☐ Walk
- ☐ Structured home exercise
- ☐ Structured exercise at a facility
- ☐ Housework
- ☐ Swimming
- ☐ Do it yourself
- ☐ Cycling
- ☐ Gardening
- ☐ Dancing
- ☐ Sport/individual
- ☐ Sport Team
- ☐ Occupational
- ☐ Other

Smoking quit date, exercise and smoking desire

Treatment session start time:	____ hh:mm
Inform the participant that they have been allocated to the physical activity group and briefly remind them what this will entail	☐
Agree a quit date	☐
Give leaflet about smoking cessation.	☐
Advise patient to identify situations when they are most likely to smoke, and to think of how they are going to address them.	☐
Physical activity group only:	
Explain how to use treadmill, recommend a Rating of Perceived Exertion (RPE) of 12-14 and explain the talk test:	☐
Agree a target for the number of minutes of treadmill walking for this session.	☐
Ask woman to exercise on treadmill for between 15-30 minutes	☐

Immediately before exercise (*for those in the control group this was asked immediately before the behavioural support*):
How strong is your desire to smoke right now?

Not at All strong			Somewhat strong			Extremely strong
1	2	3	4	5	6	7

Record time walking on treadmill	____ minutes

Immediately after exercise ask: (*for those in the control group this was asked immediately*

after the behavioural support): How strong is your desire to smoke right now?						
Not at All strong			Somewhat strong			Extremely strong
1	2	3	4	5	6	7
Discuss: benefits of exercise & barriers, aim to progress towards a target of at least 30 minutes a day or 10, 000 steps, how to use pedometer					☐	
Give patient activity diary (including steps diary), ask them to fill it in each day this week, and to bring it to the next session.					☐	
Book further appointments and give appointment card					☐	
Give £7 travel expenses and ask them to sign for it					☐	

Treatment session end time:	____ hh:mm
Length of treatment session	____ minutes

Additional questions asked post quit day only

Have you smoked at all since your quit day?			
1. No not even a puff	2. Yes just a few puffs	3. Yes between 1 and 5 cigarettes	4. Yes more than 5 cigarettes
If you have smoked more than 5 cigarettes and have returned to smoking on a daily basis, how many cigarettes are you currently smoking **each day**?			

Have you used any Nicotine Replacement Therapy (NRT) this week?	YES / NO
Which type of NRT have you mainly used?	☐ Not Applicable ☐ Patch ☐ Gum ☐ Inhalator ☐ Lozenge ☐ Tablets ☐ Nasal Spray

How many days approximately have you used NRT in the past week?						
N/A	1 day	2 days	3 days	4 days	5 days	6 days

End of pregnancy behavioural support question:

Besides the help we have given you, have you received any face-to-face support for stop smoking during your pregnancy? Yes/no
If yes, approximately how many sessions have you attended?

Antenatal complications and birth out comes

Woman's age at delivery ☐ years

Number of Births

Has there been multiple births (e.g. twins or triplets)?	Yes/ No
If yes, please state the number of births/infants:	
Maternal death:	Yes/ No
If yes, please state date of death:	☐ *dd-mmm-yyyy*

Antenatal complications

Gestational hypertension/Pregnancy induced hypertension (PIH):	Yes/ No
Pre-eclampsia (PET):	Yes/ No
Intrauterine growth restriction (IUGR):	Yes/ No
Details of IUGR: Date of diagnosis	☐ *dd-mmm-yyyy*

Baby 1 (scan @ 20 weeks)	
Abdominal circumference:	☐ *mm*
Head circumference:	☐ *mm*
Femur length:	☐ *mm*

Baby 2 (scan @ 20 weeks)	
Abdominal circumference:	☐ *mm*
Head circumference:	☐ *mm*
Femur length:	☐ *mm*
Baby 3 (scan @ 20 weeks)	
Abdominal circumference:	☐ *mm*
Head circumference:	☐ *mm*
Femur length:	☐ *mm*

• Antepartum haemorrhage (APH) requiring hospital admission Yes ☐ No ☐

Incident No.	Date (dd/mmm/yyyy)	Gestation Weeks	Days	Duration (Days)	Amount *	Cause of APH**
1						
2						
3						
4						

* Options for AMOUNT:

-Spotting

-Light

** Options for CAUSE of APH:

-Unknown

-Placenta Praevia

- Urinary tract infection (UTI) in pregnancy Yes ☐ No ☐
  If yes (UTI), how many? ☐
- Other infection in pregnancy Yes ☐ No ☐
- Oligohydramnios Yes ☐ No ☐
- Polyhydramnios Yes ☐ No ☐
- Congenital malformation Yes ☐ No ☐
  If yes, give type of malformation: ☐
- Premature rupture of membranes (PROM)? Yes ☐ No ☐
- Prelabour rupture of membranes? Yes ☐ No ☐
- Number of antenatal day unit (ADU) attendances ☐

Reason(s) for antenatal attendance (tick all that apply):		
☐ Abdominal pain	☐ Growth scan	☐ Severe headaches
☐ Itching	☐ Reduced fetal movement	☐ Vaginal (PV) bleeding not req. admission
☐ Fainting/dizziness	☐ Spontaneous rupture of the membranes (SROM)	☐ Chest pain/shortness of breath
☐ Intramuscular (I/M) iron administration	☐ Generally unwell	☐ Obstetric cholestasis (OC)

☐ External cephalic version (ECV)	☐ Urinary tract infection (UTI)	☐ Anti-D administered
☐ PET screen	☐ Scoliosis	☐ Symphysis pubis dysfunction (pelvic girdle problems)
☐ Cardiotocography (CTG)	☐ Membrane sweep	
☐ Other reasons:		

- Hospital admissions overnight for women to antenatal ward: ☐ nights

Birth outcome data

Labour

• Onset of labour:

- Spontaneous
- Induced
- Augmented
- No labour – Elective c/s (caesarean)
- No labour – Emergency c/s

• Pain relief*: (tick all that were taken)*

- Water
- Tens
- Entonox (Gas & air)
- Opiate
- Epidural
- Spinal
- General anaesthetic (GA)
- General anaesthetic (GA) following failed epidural/spinal
- Combined spinal-epidural (CSE)

• Mode of delivery:

- Spontaneous vaginal delivery (SVD)
- Assisted vaginal breech
- Ventouse
- Forceps
- Elective c/s (caesarean)
- Emergency c/s
- Semi-elective c/s (i.e. elective brought forward as an emergency)

1 . ☐

2. ☐

3. ☐

• Reason for c/s:

- Not applicable
- Not available

- Previous c/s
- Failed induction of labour (IOL)
- Fetal distress
- Failure to progress
- Placenta praevia
- Antepartum haemorrhage (APH)
- Failed instrumental
- Poor obstetric history
- Failed external cephalic version (ECV)
- Macrosomia
- Pre-eclampsia (PET)
- Obstetric cholestasis (OC)
- Multiple pregnancies
- Abdominal Cerclage
- Breech
- Fetal abnormality
- Previous 3rd or 4th degree tear
- Placental abruption
- Unstable lie
- Maternal medical condition
- Maternal request/tocophobia
- Suspected scar dehiscence
- Uterine rupture
- Cervical fibroid covering internal os
- Previous gynae. surgery
- Cord prolapse
- Severe symphysis pubis dysfunction (pelvic girdle problems)
- History of back injuries
- Orthopaedic complication restricting induction
- Cephalopelvic disproportion

• Duration of 1st stage of labour ☐ minutes

• Duration of 2nd stage of labour ☐ minutes

• Duration of 3rd stage of labour ☐ minutes

☐ ☐

• Total duration of labour hours minutes

Duration of ruptured membranes:	
	☐ *weeks* ☐ *days* ☐ *hours*

• Blood loss at delivery ☐ mls ☐ estimated ☐ measured ☐ both

Outcomes for infant

If birth did not take place**:**

• Maternal death Yes ☐ date ☐

dd-mm-yyyy

• Fetal outcome:

- *Alive* *Baby 1.* ☐
- *Fetal death In utero <24 weeks* *Baby 2.* ☐
- *Fetal death In utero >24 weeks* *Baby 3.* ☐
- *Intrapartum death (i.e. at delivery)*
- *Neonatal death* ☐

• Date of delivery of baby (dd/mm/yyyy)

• Time of delivery of baby ☐ : ☐ (hh:mm)

• Gestational age at delivery ☐ + ☐ (weeks + days)

• Age of mother at delivery ☐ (years)

• Number of fetuses ☐

• Baby(ies) sex

1. Male
   Female

2. Male
   Female

3. Male
   Female

• Baby(ies) birth weight

1 . ☐ grammes

2. ☐ grammes

3. ☐ grammes

• Customised birth weight centile
(to be calculated using desktop programme)

1 . ☐

2. ☐

3. ☐

• Placental weight ☐ grammes Unknown ☐

• Baby(ies) head circumference 1. ☐ mm 2. ☐ mm 3. ☐ mm

- Baby(ies) length 1. ☐ mm 2. ☐ mm 3. ☐ mm

- 1 minute Apgar score 1. ☐ 2. ☐ 3. ☐

- 5 minute Apgar score 1. ☐ 2. ☐ 3. ☐

- Resuscitation:

1. Yes ☐ No ☐

2. Yes ☐ No ☐

3. Yes ☐ No ☐

- Baby(ies) cord pH - arterial:

1. ☐

2. ☐

(Record information for twins, but cord pH not recorded for multiple births.)

- Baby(ies) cord pH - venous:

1. ☐

2. ☐

- Admission to neonatal intensive care unit (NICU)/special care baby unit (SCBU)

Yes ☐ No ☐

- Hospital admissions overnight for women to postnatal ward ☐ nights

- Total nights admitted to hospital ☐ nights

(calculated by totalling antenatal nights (see page 3.) and postnatal nights in hospital)

• Feeding at hospital discharge:

Infant 1

- Exclusively breastfed
- Mixed feeding
- Exclusively infant formula

Infant 2

Exclusively breastfed

- Mixed feeding
- Exclusively infant formula

Infant 3

Exclusively breastfed

- Mixed feeding
- Exclusively infant formula

Appendix 7 Statistical analysis plan

Version no. 1.0

Date: 7th November 2012

Full trial title: A pragmatic randomised controlled trial of physical activity as an aid to smoking cessation during pregnancy

Acronym: London Exercise And Pregnant smokers (SNAP) trial

International Standardised Randomised Controlled trial Number: ISRCTN48600346

Trial sponsor: St George's University of London

Chief investigator: Professor Michael Ussher

Analysis Plan prepared by: Professor Michael Ussher, Professor Sarah Lewis,

Nominated statisticians for analysis: Professor Sarah Lewis, Professor Michael Ussher, Muhammad Riaz

Projected start date: 1st April 2009

Recruitment to be completed: end of Nov 2012

Expected completion date: July 2013 (primary endpoints)

Published Trial protocol: Ussher et al (2012) Physical activity as an aid to smoking cessation during pregnancy (LEAP) trial: study protocol for a randomized controlled trial. Trials, 13(1):186.

1. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

1.1 Objectives and aims

The LEAP trial will investigate whether or not a physical activity intervention plus behavioural support is more effective than behavioural support alone (control) in achieving smoking cessation at 'end of pregnancy' for women who are between 10 and 24 weeks pregnant, who currently smoke 1 or more cigarettes daily and who smoked 5 or more cigarettes daily before pregnancy. We will also determine the cost-effectiveness of the intervention.

1.2 Trial configuration: Multicentre, parallel group with 1:1 allocation between physical activity and control.

1.3 Randomisation procedures

1.3.1 Points of randomisation and the baseline visit

After confirming eligibility, informed consent for trial entry is sought. After consenting to trial entry, women are randomised. Randomisation is via the Nottingham Trials Unit web-based database and randomisation service. In each centre the recruiting research midwife (RM) has a username and password. She logs on to the trial website that hosts the trial database confirms that the patient eligibility criteria are all met and enters *registration* data about the participant and centre before randomisation is possible. The computer then issues a trial number, which is a unique identifier for the trial participant, and a treatment allocation code.

1.3.2 Specify block size, whether randomly varied

Random permuted blocks of randomly varying size.

1.3.3 Stratified allocation, or post-stratified analysis

Randomisation is stratified by trial centre only.

1.4 Allocation concealment:

As this is a behavioural intervention, there is no allocation concealment for participants or researchers.

1.5 Stopping rules determined as part of the protocol

Stopping rules have not been specified.

1.6 Outcomes

1.6.1 Primary outcome

The primary outcome is self-reported, continuous abstinence from smoking between the quit date and end of pregnancy, validated by exhaled carbon monoxide (CO) or salivary cotinine.

Continuous abstinence is defined as having smoked less than 5 cigarettes since the quit day.

Exhaled CO: The criteria for confirming abstinence is a reading of <8ppm.

Salivary cotinine: The criteria for confirming abstinence is a value of <10ng/ml.

End of pregnancy: It is acceptable for this measure to be taken at a follow-up up to 4 weeks before birth, at delivery, or within 10 weeks after the birth.

The primary outcome is dichotomous; i.e. abstinent or non-abstinent.

For a participant to be classed as abstinent from smoking at end of pregnancy (i.e. positive primary outcome)**:**

At 4 weeks post-quit (It is acceptable for this measure to be taken between 25 days to 6 weeks post-quit): [a]

Have you smoked at all since your quit day?= 'No not even a puff' or 'yes just a few puffs' or 'Yes, between 1 and five cigarettes' or 'missing' [a] (i.e. any response other than 'yes, more than 5 cigarettes')

AND CO is <8ppm

AND/OR cotinine is <10ng/ml

OR CO or cotinine is missing[b]

AND

At end of pregnancy:

Have you smoked at all since your quit day?= 'No not even a puff' or 'yes just a few puffs' or 'Yes, between 1 and five cigarettes' (i.e. any response other than '5 or more cigarettes')

AND CO is <8ppm[b]

AND cotinine is <10ng/ml[c]

For a participant to be classed as non-abstinent from smoking at end of pregnancy (i.e. negative primary outcome)**:**

At 4 weeks or end of pregnancy:

- Have you smoked at all since your quit day?= 'yes, more than 5 cigarettes'

- CO or salivary cotinine values do not confirm abstinence.

- Has withdrawn from the study (i.e. refuses follow-up).

- Fails to set a quit date which the follow-up assessment can be referenced against.

At end of pregnancy:

- Refuses to allow biochemical validation

- Refuses to self-report number of cigarettes smoked.

- Unable to contact in order to confirm smoking status (i.e. lost to follow-up).

---

[a]Some women will not have data for self-report of smoking or biochemical validation at 4 weeks. If these women are confirmed as abstinent at end of pregnancy it will be considered as a positive primary outcome. All those classed as abstinent at end of pregnancy will automatically be classed as abstinent at 4 weeks post-quit.

[b]Some participants will only have CO or cotinine and, for these women, a reading in the stated range is defined as a positive primary outcome (even without the reading for the other biochemical measure). Most participants will have both CO and cotinine and, for these women, BOTH readings must fall within the defined ranges to count as a positive outcome.

[c]If a new normative value becomes available during the trial this will be used.

1.6.2 Secondary outcomes

Included in paper reporting primary outcomes:

a) Smoking abstinence

Self-reported, continuous abstinence from smoking (up to 5 cigarettes allowed) between quit date and 4 weeks, with biochemical validation (to compare success rates with NHS standards).

b) Physical activity

1. Self-reports of physical activity levels at 1, 4 and 6 weeks after the quit date and at end of pregnancy. Also, at each time point, the numbers reporting walking as the main physical activity.

2. Record of duration of time on treadmill, during supervised exercise.

3. Accelerometer record (Actigraph) of minutes of at least moderate intensity physical activity, during the first week after the quit date. This data is only for 10% of participants.

4. Among those in the exercise group, record of pedometer steps (among those choosing to wear a pedometer at 1, 2, 3, 4, 5 and 6 weeks after the quit date.

c) Aids to smoking cessation

1. Use of nicotine replacement

2. Use of behavioural support other than that provided in the trial

Included in other papers:

a) Smoking abstinence

1. Self-reported, continuous abstinence from smoking (up to 5 cigarettes allowed) between quit date and 6 months after delivery (no biochemical validation).

2. Among those women who relapse, levels of smoking reduction between baseline and end of pregnancy.

3. Lapse free smoking abstinence between quit date and 4 weeks and end of pregnancy (both biochemically validated) and between quit date and six months (without validation).

b) Physical activity

Self-reports of physical activity levels at six months after the birth

c) Psychological outcomes

1. Weekly urges to smoke at baseline and 1, 2, 3 and four weeks after the quit day.

2. Daily urges to smoke on each day in the first week following the quit day.

3. Desire to smoke before and after supervised exercise weekly up to 4 weeks after the quit day.

4. In control group only: Desire to smoke before and after smoking cessation counselling weekly up to 4 weeks after the quit day.

5. Tobacco withdrawal symptoms at baseline and 1 and 4 weeks after the quit day.

6. Self-confidence in stopping smoking at baseline, 1 and 4 weeks after the quit day, end of pregnancy and 6 months after the birth.

7. Self-confidence for maintaining regular physical activity at baseline, 1 and 4 weeks after the quit day, end of pregnancy and 6 months after the birth.

8. Self-reported depression at end of pregnancy and 6 months after the birth.

d) Maternal weight

Maternal gestational weight at baseline, 4 weeks after the quit day and end of pregnancy. (Some of the end of pregnancy measures may be up to 10 weeks after the birth).

e) Fetal loss and morbidity and other fetal and birth outcomes

The following perinatal measures are extracted from patient's hospital records: (i) antenatal complications, including any admissions and the reasons for the admissions, (ii) gestation at onset/induction of labour (and indication for induction where appropriate), (iii) duration of labour and mode of delivery, (iv) Apgar scores of infants, and where available acid-base status of infants, and rates of transfer to the neonatal intensive care unit, (v) birth weight and placental weight.

1. Miscarriage (non-live birth prior to 24 weeks gestation) and stillbirth (non-live birth at 24 weeks gestation or later)
2. Intrapartum death (i.e. at delivery)
3. Neonatal death (i.e. from live birth to 28 days)
4. Intrauterine growth restriction (IUGR)
5. At 20 week scan, abdominal circumference, head circumference, femur length
6. Oligohydramnios (deficiency of amniotic fluid)
7. Polyhydramnios (excess of amniotic fluid)
8. Congenital malformation (and type of malformation)
9. Individualized birth weight Z score (i.e. birth weight adjust for gestational age, maternal height, maternal weight at booking and ethnic group).
10. Unadjusted birth weight and birth weight as Z-score
11. Apgar score
12. Cord blood pH
13. Gestational age at birth
14. Intraventricular haemorrhage
15. Neonatal enterocolitis
16. Neonatal convulsions
17. Congenital abnormality
18. Neonatal intensive care unit (NICU) admission
19. Infant ventilated > 24 hrs
20. Elective termination
21. Elective termination undertaken for fetal morbidity judged incompatible with fetal / infant survival

f) Maternal morbidity and mortality and other maternal outcomes

1. Maternal mortality
2. Gestational hypertension/Pregnancy induced hypertension (PIH)
3. Pre-eclampsia (PET):
4. Antepartum haemorrhage (APH) requiring hospital admission
5. Urinary tract infection (UTI) in pregnancy (and number of infections)
6. Pre-labour rupture of membranes at pre-term (i.e. before 37 weeks) (PPROM)
7. Pre-labour rupture of membranes at term (i.e. 37 weeks onwards) (PROM)
8. Number of antenatal day unit (ADU) attendances
9. Hospital admissions overnight for women to antenatal ward:
10. Reason/s for antenatal attendance
11. Other antenatal complications
12. Onset of labour (e.g. induced)
13. Pain relief
14. Mode of delivery
15. If caesarean section, reason for CS
16. Duration of three stages of labour and total duration of labour
17. Duration of ruptured membranes
18. Blood loss at delivery
19. Proteinuria

g) Health economic data

1. Duration of maternal hospital admission for childbirth

2. Duration of any admission (of baby) to special care

1.7 Determination of Sample Size

A Cochrane review suggests that approximately 9% of women who are still smoking at the time of their first antenatal visit will stop smoking with usual care through to the end of their pregnancy, and a further 6% will stop as a result of a smoking cessation programme using individual behavioural support. Thus, in our control group we expect a smoking cessation

rate of around 15% at the end of pregnancy. Combining our pilot studies 25% (8/32) of participants in the treatment group sustained continuous smoking abstinence to the end of pregnancy. Therefore in the trial we conservatively estimate an abstinence rate of 23% at end of pregnancy in the treatment group, which would be similar to the effect shown for NRT with non-pregnant smokers [14]. We aim to recruit 433 women to each arm to detect the above absolute difference (8%) in smoking cessation rates between the groups at end of pregnancy with a two-sided significance level of 5% and a power of 83%. This calculation is based on a chi-squared test with Yate's correction.

1.8 Protocol amendments that have statistical implications should be described.

For the follow-up at end of pregnancy the valid period for assessment was originally defined as 38 weeks gestation to two weeks after the birth. This was revised to 36 weeks gestation to 10 weeks after the birth.

2. ANALYSIS CONSIDERATIONS

2.1 Analysis for primary outcome

Initially, we will conduct a descriptive comparison of the baseline characteristics of the two treatment groups. Our primary outcome measure, continuous abstinence from smoking from quit date to end of pregnancy, will be compared between treatment groups using logistic regression, adjusted for recruitment centre only, with statistical significance determined by the likelihood-ratio test and with the estimate of effect given as the odds ratio and 95% confidence interval. Our primary analysis will not adjust for any further variables since effect estimates can be sensitive to decisions concerning what variables to adjust for and how these are specified. Nevertheless, the adjustment for baseline covariates is often advised. First, to correct for any chance imbalances in important prognostic variables following randomisation and secondly, because adjusting for highly important prognostic variables in an RCT can improve the precision of treatment effect estimates even when the outcome measure is binary (Robinson, 1991). Statistical testing for baseline imbalances is not advised and instead key covariates should be selected prior to analysis based on the likely magnitude of the association with the outcome measure. Therefore as a sensitivity analysis treatment effects will be reported adjusting for the following variables in addition to centre:

(i) Nicotine dependence score at baseline (Fagerstrom Test of Cigarette Dependence Score, FTCD)

(ii) Age of finishing full time education (in years), as a proxy for socioeconomic status. For a small number of women still in full time education at the time of enrolment the participant's current age will be used instead of age of finishing education.

(iii) maternal age at baseline

(iv) Depression score at baseline (Edinburgh Post-natal Depression Scale, EPDS)

(v) Partner's smoking status (This was not specified in the published protocol, see section 6, p.8 of this SAP).

If we observe differences between the two groups in use of NRT, or use of behavioural support outside of the intervention sessions, then we will conduct a sensitivity analysis to examine the effect of controlling for any differences between groups in these variables. We will analyse other binary smoking outcomes in a similar way.

2.2 Unit of analysis considerations

For outcome measures relating to smoking cessation the women randomised will represent the unit of analysis. All other outcomes will be related to these women, except those related to the offspring (e.g. birth weight), in which case the offspring will be the unit of analysis instead. A small number of children will be born as multiple births (e.g. twins) and data for these cases will be clustered rather than independent. The primary analysis will be of singleton births and we will carry out a sensitivity analysis, including multiple births allowing for the clustering of outcomes. More specifically:

Outcomes where the offspring is the unit of analysis will comprise singleton births only to allow for the fact that observations will be non-independent and that non-singleton births are likely to have very different birth outcomes in any case. In a subsidiary analysis multiple births will be included and clustering accounted for using an approach previously published (Gates S & Blocklehurst P, 2001). This adapts methodology previously created for use with cluster randomised RCTs, assuming that each women is regarded as the 'cluster' and her number of offspring the cluster size.

2.3 Effect modification and sub-group analyses

For our primary outcome, if the intervention is effective, we will look for effect modification by age at leaving full time education and baseline levels of physical activity. Our multiple logistic regression models will therefore be augmented with appropriate interaction terms. Initially, both age at leaving education and baseline physical activity will be fitted as continuous terms to maximise power when testing for an interaction. If evidence of an interaction is present (taken as a p-value of < 0.05) then further subgroup analyses will dichotomise these variables (at the median) for ease of interpretation. The purpose of these models is to establish whether women with low or high levels of education, or high or low baseline levels of physical activity, could benefit preferentially from a physical activity intervention. If there is evidence of interaction, we will perform subgroup analysis of the efficacy of PA compared with usual care in subgroups defined by levels of age at leaving full-time education and by levels of baseline physical activity.

2.4 Analysis for secondary outcomes (not in main paper)

We will compare secondary outcomes, including urges to smoke, withdrawal symptoms, self-confidence and PA, in the first week of abstinence, and the same variables and maternal gestation weight and depression, over subsequent time points, using mixed effects modelling to allow for repeated measures, with adjustment for centre. To deal with non-normally distributed variables we will use transformations to normality, residual bootstrapping, or dichotomising. Differences between groups in perinatal outcomes, including birth-weight and gestation, mode of delivery and complications, will be analysed by linear or logistic regression, with adjustment for centre.

2.5 Timing of analyses

Baseline data with be complete in November 2012 and the baseline characteristics of the sample will then be analysed using descriptive statistics and the results will be presented in tables.

There will be two further main phases of analyses. The first will be begin around July 2013, once the end of pregnancy follow-ups are complete. The second will be conducted for data at

six months after delivery and this analysis will commence around February 2014. Data collected for secondary outcomes will not be analysed until the trial has ended with respect to the primary outcome measure.

2.6 Analysis populations and missing data conventions

Analysis will be on an intention-to-treat (ITT), that is, including all those women randomised to physical activity or usual care. Participants who, for any reason, have missing outcome data on the primary outcome or any secondary smoking outcomes, will be assumed to have resumed smoking.

We will determine the quantity and distributions of missing data. We will carry out a complete case analysis, and we will compare this with an analysis using multiple imputation to deal with missing values, which assumes data is missing at random, describing any differences in terms of the likely biases in the data. The exception is smoking outcomes, where those with missing data will be assumed to have resumed smoking.

2.7 Protocol Deviations

Failure to attend treatment sessions will not constitute a protocol deviation. The only possible protocol deviation is: Women who choose to withdraw from the trial, and choose not to consent for the use of their data for primary or secondary outcomes.

2.8 Derived variables:

Low birth weight – births of <2500g

Preterm birth – births of < 37 weeks gestation

Post-randomisation fetal death - a composite measure of all fetal deaths after randomisation– ***defined as*** – all [miscarriages + stillbirths + neonatal deaths + elective terminations conducted for fetal abnormalities judged inconsistent with fetal / infant life].

Perinatal deaths (a composite measure of all infant deaths following live births) – ***defined as*** – all [stillbirths + neonatal deaths]

2.9 Treatment Compliance and mediation analysis

We will compare compliance between the PA and control groups in terms of the percentage of treatment sessions attended. If the intervention is effective, we will use mediation analysis to examine whether there is evidence that the change in PA levels is the likely causal factor in determining smoking abstinence. We will examine the association between treatment group and change in PA levels, and the association between level of PA and abstinence. Finally, we will include level of PA in a logistic regression model of the association between treatment group and abstinence, with mediation assessed using MacKinnon's causal steps criteria.

2.10 Software used

We will use STATA version 11.

2.11 Levels of significance

All tests will be two-tailed, using a p value of < 0.05 to indicate statistical significance, and 95% confidence intervals will be calculated.

2.13 Format of electronic files for archiving

Excel and SPSS

3. ANALYSIS OF PARTICIPANT CHARACTERISTICS

3.1. Describe methods used to summarise data.

Continuous data that are approximately normally distributed will be summarised in terms of the mean, standard deviation, median, minimum, maximum and number of observations. Skewed data will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. Categorical data will be summarised in terms of frequency counts and percentages.

3.2. Disposition

We will summarise the number of patients screened for entry, excluded prior to randomisation by major reason and overall, the number of patients randomised and the number entering and completing each phase of the study by treatment group and overall. We will use a CONSORT flow chart for this.

3.3. Baseline

We will summarise demographic variables (e.g. age, daily number of cigarettes prior to delivery and currently, gestational age at randomisation, exhaled CO, ethnic group, education, parity, etc) by treatment group.

4. ANALYSIS OF ADVERSE EVENTS

The number of adverse events and serious adverse events will be compared between the two groups. There is unlikely to be sufficient adverse events to warrant these being reported in a table.

5. LIST OF PROPOSED SUMMARY TABLES

The proposed tables to be included in the main publication are presented below. We will also produce a CONSORT flow diagram showing exclusions, enrollment and evaluable participants.

6. Changes to statistical analysis plan relative to published protocol

After further statistical review, we request that the TSC approve the following amendment:

1. 'Partners smoking status' has been consistently related to success at quitting smoking in pregnant women and we proposed adjusting for this variable (see section 2.1 above).

2. Section 2.3 'Effect modification and sub-group analyses' was not specified in the protocol and, if the intervention is effective, we propose including this analysis.

Demographic and smoking characteristics

(give ranges for all variables)	Exercise group n= Mean (SD)	Control group n= Mean (SD)
Age (years) (range)		
Age at leaving full-time education		
BMI (kg/m^2)		
Weight (kg)		
Gestational age (weeks)		
Cigarettes smoked daily before pregnancy		
Cigarettes smoked daily at randomization		
FTCD score		
Expired carbon monoxide (ppm)		
EPDS score		
Weekly minutes of PA of at least moderate intensity		
	n/%	n/%
Married or living with partner		
Caucasian†		
Professional/managerial occupation		
Smoked in a previous pregnancy		
Parity§ 0-1 2-3 ≥4		
Previous preterm birth††		
Women with partner who smokes		
High confidence for quitting smoking (rated as very or extremely high)		
Takes alcohol ≥ twice a week		

Consumes ≥3 alcoholic drinks on a drinking day		
EPDS score ≥12		
High confidence for PA (rated as very or extremely confident)		
Positive expectation for benefits of PA for quitting (rated as moderate or large positive effect)		

FTND=Fagerstrom Test of Cigarette Dependence EPDS=Edinburgh Post-natal Depression Scale; PA=Physical Activity; BMI=Body Mass Index

† Race or ethnic group was self-reported. Race was categorized according to standard U.K. Census categories.

§ Parity was defined as the number of previous pregnancies that had progressed beyond 24 weeks.

¶ Data exclude XX women in the PA group and XX in the conytrol group who had no partner.

†† Previous preterm birth was defined as any previous pregnancy that lasted from 24 to 37 weeks.

Compliance

	Exercise group n= Mean (SD)	Control group n= Mean (SD)
Time walked on treadmill during supervised exercise Baseline one week post-quit 4 weeks post-quit 6 weeks post-quit		NA
Self-reported weekly minutes of physical activity of at least moderate intensity Baseline one week post-quit 4 weeks post-quit 6 weeks post-quit end of pregnancy		
	n/n %	n/n %
Treatment sessions attended		

Primary and secondary abstinence outcomes

Outcome	**Exercise group (N=)** Number (percent)	**Control (N=)** Number (percent)	**Odds Ratio (95% CI) †**	**Adjusted Odds Ratio (95% CI)**
Primary Self-reported continuous abstinence[a] at end of pregnancy[b] with biochemical validation[c]§				
Secondary Self-reported continuous abstinence for 4 weeks after quit day with validation†				

† Odds ratios were adjusted for recruitment center only (as a stratification factor).
‡ Odds ratios were adjusted for center, Fagerstrom Test of Cigarette Dependence score at baseline, partner's smoking status and age at leaving full-time education.
[a]Continuous abstinence is defined as having smoked less than five cigarettes since the quit day.
[b]End of pregnancy is defined as between 36 weeks gestation and 10 weeks after the birth.
[c]Validated by either exhaled carbon monoxide or salivary cotinine.
§The biochemical tests did not validate the report of not smoking (i.e., probable false reporting of cessation) in X of X women (X%) in the physical activity group and in X of X (X%) receiving usual care alone.
†§The biochemical tests did not validate the report of not smoking (i.e., probable false reporting of cessation) in X of X women (X%) in the physical activity group and in X of X (X%) receiving usual care alone.

Appendix 8 Patient and public involvement

The LEAP trial was preceded by pilot work[30] during which pregnant smokers and ex-smokers were interviewed concerning the recruitment methods, study design and interventions. The findings from these interviews were used in the design of the LEAP trial.

The Trial Steering Committe (TSC) included a lay member who approved the protocol and checked the patient information sheet and consent form, as well as being involved in monitoring all stages of the study. This individual was also involved in discussions concerning the dissemination of the findings.

The LEAP trial included qualitative interviews with women who were enrolled in the trial and with researchers delivering the interventions. This helped us to assess the acceptability of the intervention and women's overall experience of being involved in the trial. These interviews also helped us to interpret the findings and to identify topics for future research.

Appendix 9 Supplementary data on adverse events

Serious adverse events

Physical activity group

- Maternal AEs (105 events): early labour ($n = 13$), fainting/dizziness ($n = 9$), nausea or vomiting ($n = 8$), symphysis pubis dysfunction ($n = 8$), severe headaches ($n = 7$), chest pain ($n = 6$), obstetric cholestasis ($n = 4$), oligohydramnios ($n = 6$), generally unwell ($n = 6$), deep-vein thrombosis ($n = 2$), group B streptococcus ($n = 3$), pelvic pain ($n = 3$), polyhydramnios ($n = 3$), vaginal discharge ($n = 3$), dermatisis ($n = 2$), incompetent cervix ($n = 2$), uterine contractions during pregnancy ($n = 2$), abnormal antibodies, abnormal blood flow to placenta, anaemia, back pain, bicornate uterus, diarrhoea, Graves' disease, hind waters rupture, palpitations, positive urine toxicology, post-partum haemorrhage, pregnancy-related tachycardia, right iliac fossa pain, sciatica, supraventricular tachycardia, thyroid problems, urinary incontinence, varicose veins (all $n = 1$).
- Fetal AEs (14 events): congenital malformation ($n = 10$), abnormal fetal heart rate ($n = 1$), fetal kidney problem ($n = 1$), unstable lie ($n = 2$).
- Neonatal AEs (15 events): premature birth at < 32 weeks ($n = 5$), congenital malformations ($n = 9$) [exomphalos ($n = 2$), talipes ($n = 2$), anomalous pulmonary venous drainage, bilateral cleft lip and palate, enlarged clitoris, perimembranous and muscular ventricular septal defect, small sacral skin tag (all $n = 1$)], shoulder dystocia ($n = 1$).

Control group

- Maternal AEs (114 events): generally unwell ($n = 11$), symphysis pubis dysfunction ($n = 11$), fainting/dizziness ($n = 10$), oligohydramnios ($n = 10$), early labour ($n = 8$), nausea or vomiting ($n = 8$), obstetric cholestasis ($n = 7$), severe headaches ($n = 6$), vaginal discharge ($n = 5$), polyhydramnios ($n = 4$), thrombocytopenia ($n = 2$), back pain ($n = 4$), diarrhoea ($n = 3$), oedema ($n = 3$), epigastric pains ($n = 2$), placental insufficiency ($n = 2$), Bell's palsy, chest pain, deep-vein thrombosis, epileptic fits, fever, group B streptococcus, irritable bowel syndrome, leaking pulmonary valve, pelvic pain, leg pain, persistent proteinuria, rectal bleeding, renal calculi, right iliac fossa pain, scoliosis, sickle cell anaemia, uterine contractions during pregnancy, vaginal pain (all $n = 1$).
- Fetal AEs (14 events): congenital malformation ($n = 9$), unstable lie ($n = 2$), abnormal fetal heart rate, static growth on scan (< 10th centile), unprovoked decelerations of fetal heart rate (all $n = 1$).
- Neonatal AEs (14 events): premature birth at < 32 weeks ($n = 9$), congenital malformations ($n = 5$) [chronic lung condition, extra toe on left foot, gastroschisis, renal dilatation of both kidneys, renal tract anomaly (all $n = 1$)].

Appendix 10 Results of subgroup cost-effectiveness analysis

The cost-effectiveness calculations were repeated using data from subgroups stratified by age and FTCD score. In each case, the population was divided approximately in half. The groups considered were age < 28 years, age > 27 years, FTCD score < 4, FTCD score ≥ 4. In this appendix the point estimate cost-effectiveness results are shown, followed by the cost-effectiveness scatterplot and cost-effectiveness acceptability curve derived from the same approach of imputation and bootstrapping as was used for the complete data set. Note that in each case there is no dominance relationship in the point estimate results but there is still considerable uncertainty shown on the cost-effectiveness plane and in the cost-effectiveness acceptability curves. A reasonable interpretation of these results is that there is no strong evidence of a subgroup effect.

TABLE 23 Results of the incremental cost-effectiveness analysis for women aged < 28 years

Group	Expected per-participant costs (£, 2012/13 prices)	Expected quit rate (%)	Expected annual costs (£, 2012/13 prices)	Expected annual quitters	ICER
PA	4472	0.0542	259,348	3.14	£84,000 per quitter. Note that this result taken in isolation would suggest that PA should be preferred at any willingness to pay *below* £84,000 per additional quitter. This is because the differences in costs and effectiveness are both negative. However, in context, a more reasonable interpretation is that there is no significant difference between the PA group results and the control group results for either cost or effectiveness
Control	4757	0.0576	275,932	3.34	
Difference	−286	−0.0034	−16,584	−0.20	

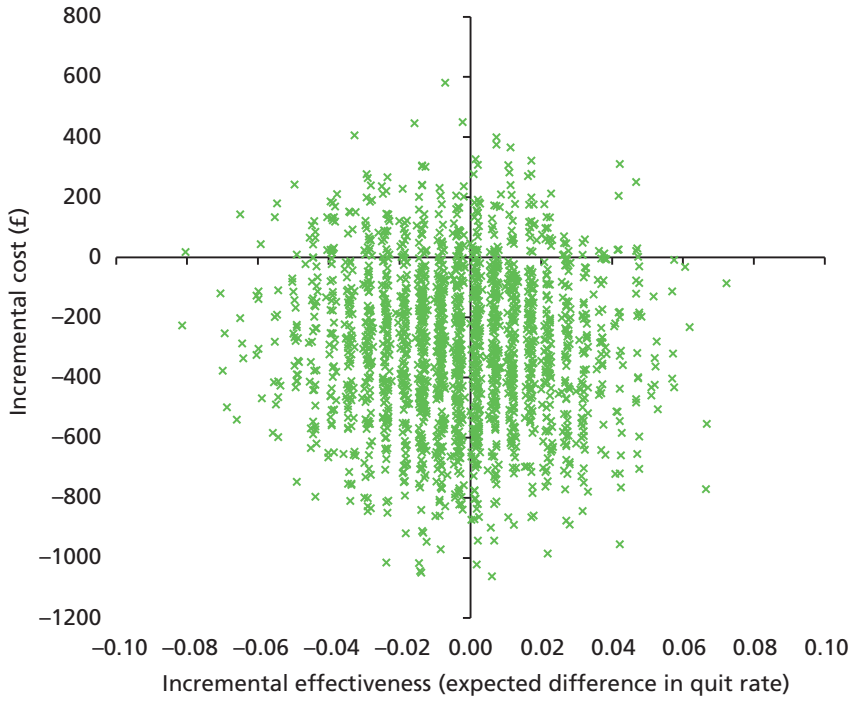


FIGURE 7 Cost-effectiveness scatterplot for women aged < 28 years.

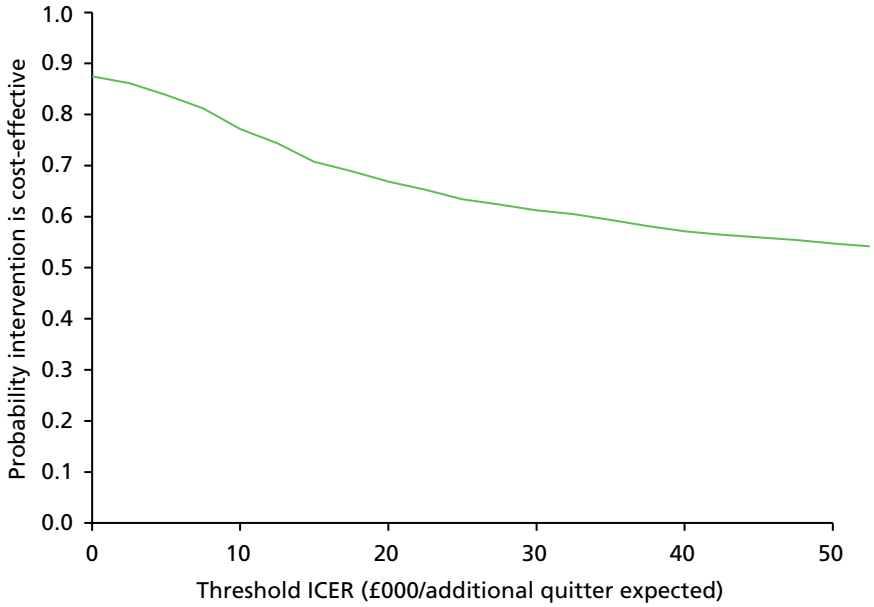


FIGURE 8 Cost-effectiveness acceptability curve for women aged < 28 years.

TABLE 24 Results of the incremental cost-effectiveness analysis for women aged > 27 years

Group	Expected per-participant costs (£, 2012/13 prices)	Expected quit rate (%)	Expected annual costs (£, 2012/13 prices)	Expected annual quitters	ICER
PA	4968	0.101	288,119	5.86	£7200 per quitter. Note that this result taken in isolation would suggest that PA should be preferred at any willingness to pay above £7200 per additional quitter. However, in context, a more reasonable interpretation is that there is no significant difference between the PA group results and the control group results for either cost or effectiveness
Control	4738	0.069	274,791	4.02	
Difference	230	0.032	13,328	1.84	

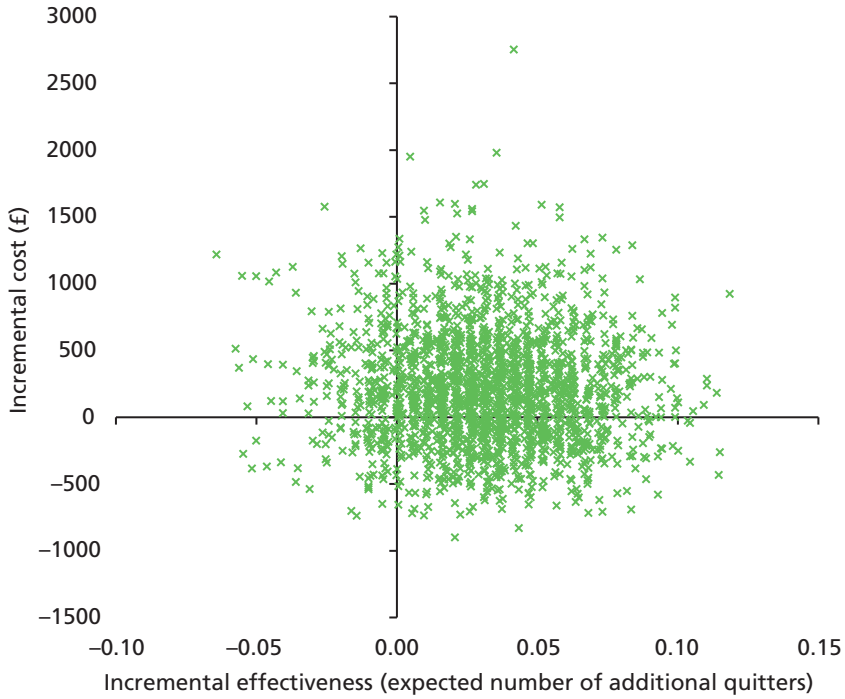


FIGURE 9 Cost-effectiveness scatterplot for women aged > 27 years.

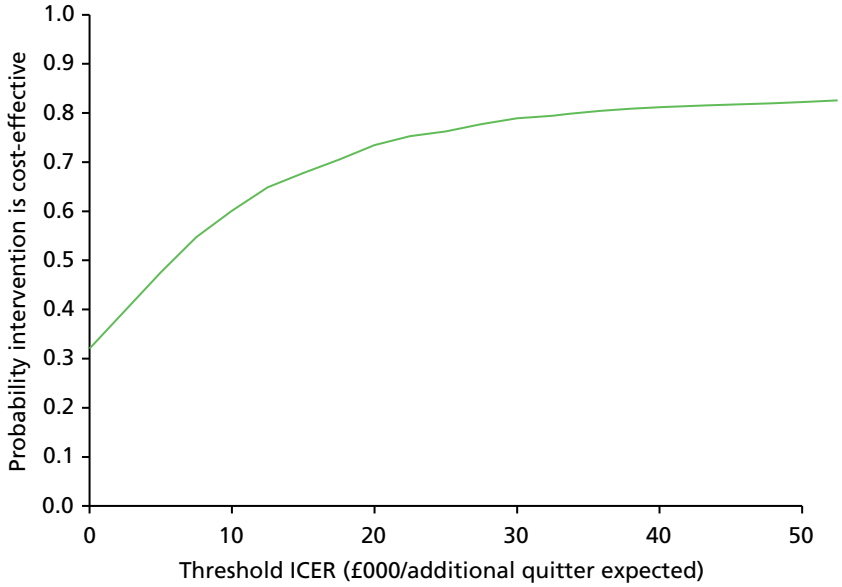


FIGURE 10 Cost-effectiveness acceptability curve for women aged > 27 years.

TABLE 25 Results of the incremental cost-effectiveness analysis for FTCD score of < 4

Group	Expected per-participant costs (£, 2012/13 prices)	Expected quit rate (%)	Expected annual costs (£, 2012/13 prices)	Expected annual quitters	ICER
PA	4620	0.122	267,945	7.06	£4900 per quitter. Note that this result taken in isolation would suggest that PA should be preferred at any willingness to pay above £4900 per additional quitter. However, in context, a more reasonable interpretation is that there is no significant difference between the PA group results and the control group results for either cost or effectiveness
Control	4435	0.084	257,242	4.89	
Difference	185	0.037	10,703	2.17	

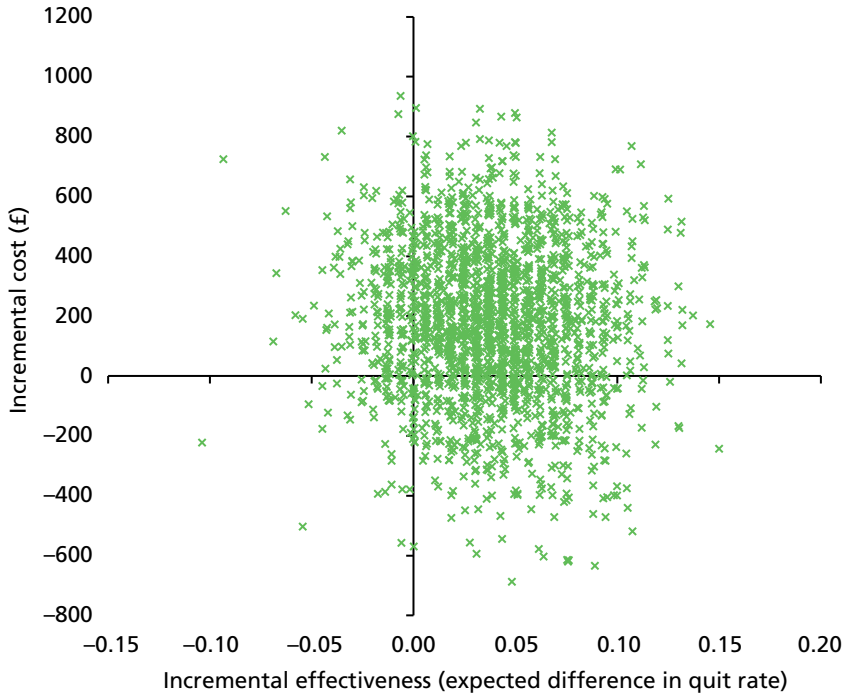


FIGURE 11 Cost-effectiveness scatterplot for FTCD score of < 4.

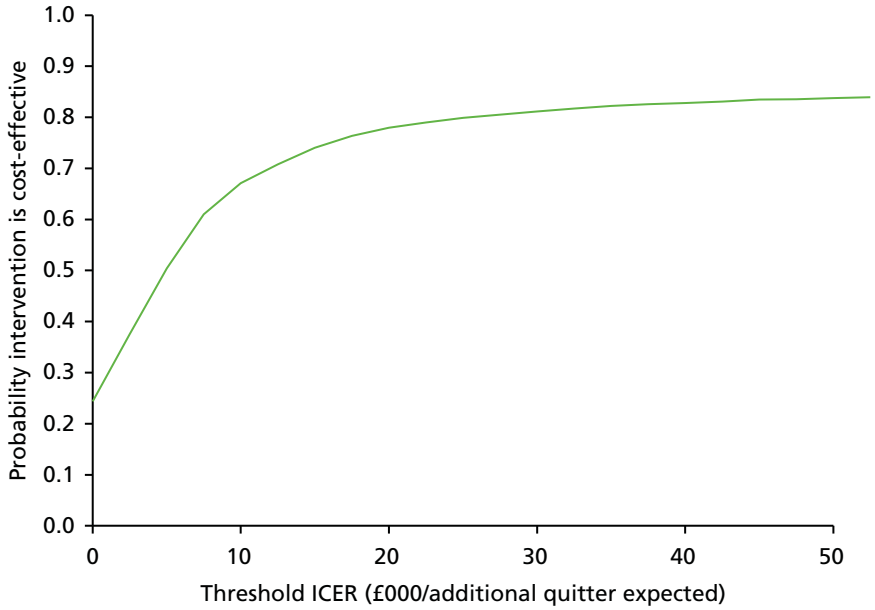


FIGURE 12 Cost-effectiveness acceptability curve for FTCD score of < 4.

TABLE 26 Results of the incremental cost-effectiveness analysis for FTCD score of ≥ 4

Group	Expected per-participant costs (£, 2012/13 prices)	Expected quit rate (%)	Expected annual costs (£, 2012/13 prices)	Expected annual quitters	ICER
PA	4772	0.0468	276,788	2.71	£124,000 per quitter. Note that this result taken in isolation would suggest that PA should be preferred at any willingness to pay *below* £124,000 per additional quitter. This is because the differences in costs and effectiveness are both negative. However, in context, a more reasonable interpretation is that there is no significant difference between the PA group results and the control group results for either cost or effectiveness
Control	4976	0.0485	288,630	2.81	
Difference	−204	−0.0016	−11,842	−0.10	

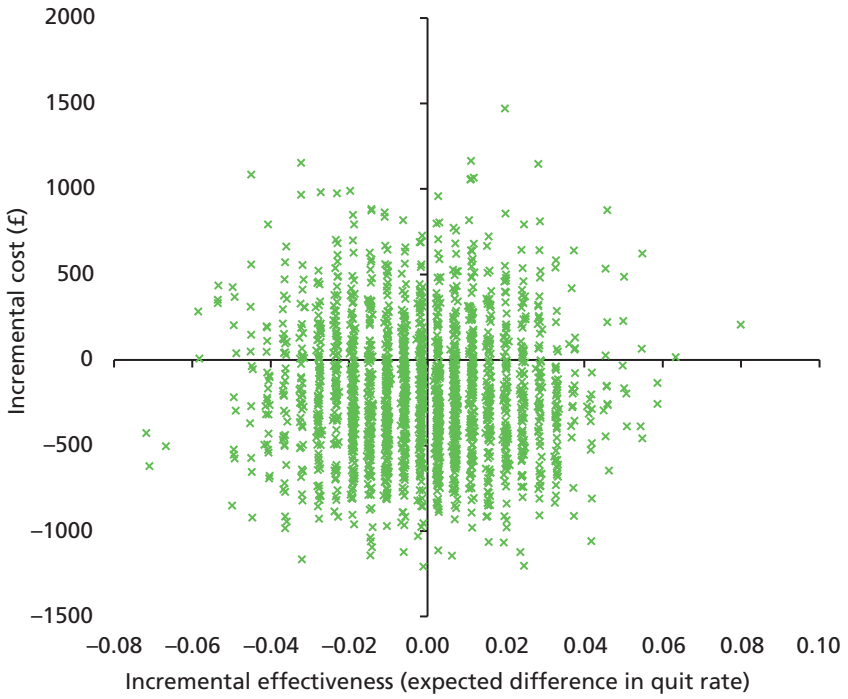


FIGURE 13 Cost-effectiveness scatterplot for FTCD score of ≥ 4.

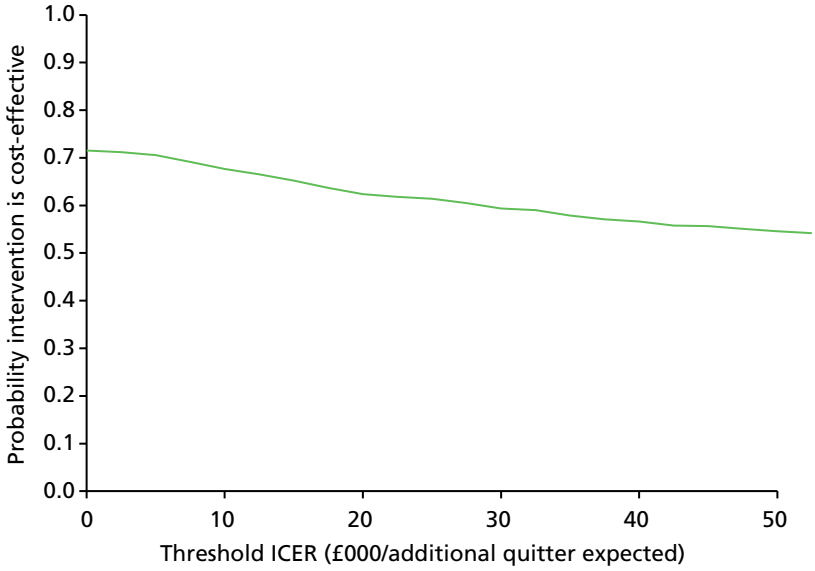


FIGURE 14 Cost-effectiveness acceptability curve for FTCD score of ≥ 4.

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